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Evaluating Health Policy and Legal Responses: How to Reduce Barriers and Improve Access to Orphan Drugs for Rare Diseases in Canada

by

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Évaluation des politiques et des mesures juridiques en santé: comment en arriver à réduire les obstacles afin d'améliorer l'accessibilité aux médicaments orphelins pour les maladies rares au Canada

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Abstract

Rare diseases are debilitating conditions often leading to severe clinical manifestations for affected patients. Orphan drugs have been developed to treat these rare diseases affecting a small number of individuals. Incentives in the legal framework aimed to recoup the research and development cost of orphan drugs for pharmaceutical companies have been implemented in the United States and the European Union. At the present time, Canada is still lacking a legal and policy framework for orphan drugs. Several problems at the federal and provincial levels remain: lack of research funds for rare diseases, discrepancies on orphan drug policies between provinces, difficulties to access and reimburse these high price drugs. Recommendations and measures are proposed, such as a pan-Canadian (national) scientific committee to establish evidence-based guidelines for patients to access orphan drugs uniformly in all provinces with a disease specific registry, a formal agreement for a centralized Canadian public funding reimbursement procedure, and increasing the role of "guardian" for prices by the Patented Medicines Review Board in Canada. These recommendations and measures will be beneficial for the implementation of a policy framework for orphan drugs in Canada.

Résumé

Les maladies rares sont des maladies sérieuses pouvant causer des manifestations cliniques sévères chez les patients atteints. Les médicaments orphelins ont été développés pour le traitement de ces maladies rares qui touchent un petit nombre d'individus. Un cadre légal permettant des incitatifs pour les compagnies pharmaceutiques aux États-Unis et au niveau de l'Union Européenne a favorisé la recherche et le développement desdits médicaments. Présentement, il n'existe pas de cadre juridique et de politiques spécifiques au Canada entourant les médicaments orphelins. Ceci a mené à plusieurs problèmes tant au niveau fédéral que provincial dont: un manque de support financier consacré à la recherche pour les maladies rares, des disparités entre les provinces concernant les politiques pour les médicaments orphelins, des difficultés d'accès et de remboursement desdits médicaments dont les coûts sont élevés. Des recommandations et mesures sont proposées, telles l'implantation d'un comité scientifique pancanadien (national) afin d'établir des lignes directrices fondées sur des données probantes pour faciliter un accès uniforme aux médicaments orphelins pour les patients, y compris un registre spécifique élaboré pour chaque maladie, établir une entente formelle centralisée pour tout le Canada pour un financement public de remboursement des médicaments orphelins, augmenter le rôle de « gardien » des prix par le Conseil d'examen du prix des médicaments brevetés au Canada. Ces recommandations et mesures serviront à l'implantation d'un cadre de politiques pour les médicaments orphelins au Canada.

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List of Abbreviations

AACT: Aggregate Analysis of Clinical Trials

ACTH: Adreno Cortico Trophic Hormone

aHUS: Atypical Hemolytic Uremic Syndrome

Board: Patented Medicine Prices Review Board

CAD: Canadian

CADTH: Canadian Agency for Drugs and Technologies in Health

CAPS: Cryopyrin-Associated Periodic Syndrome

CBA: Cost-benefit analysis

CCOHTA: Canadian Coordinating Office for Health Technology Assessment

CDEC: Canadian Drug Expert Committee

CDR: Common Drug Review

CEA: Cost-effectiveness analysis

CED: Committee to Evaluate Drugs

CEDAC: Canadian Expert Drug Advisory Committee

CFDI: Canadian Fabry Disease Initiative

CIHR: Canadian Institutes of Health Research

COMP: Committee for Orphan Medicinal Products

CORD: Canadian Organization for Rare Disorders

CSEMI: Comité scientifique de l'évaluation des médicaments pour des fins d'inscription

CUA: Cost-utility analysis

DIN: Drug Identification Number

DRD: Drugs For Rare Diseases

EAP: Exceptional Access Program

EDRD: Expensive Drugs for Rare Disease Advisory Committee

EDS: Exception Drug Status

EMA: European Medicines Agency

EPARs: European Public Assessment Reports

ERT: Enzyme replacement therapy

EU: European Union

EURORDIS: European Organization for Rare Diseases

FDA: Food and Drug Administration

HCIWG: Health Care Innovation Working Group

HIPC: Highest International Price Comparison

HTA: Health technology assessment

ICER: Incremental cost-effectiveness ratio

IIR: Investigator Initiated Research

IMD : Inherited Metabolic Diseases

INESSS : Institut national d'excellence en santé et en services sociaux

INSERM: Institut national de la santé et de la recherche médicale

IRDiRC: International Rare Diseases Research Consortium

LYG: Life-year gained

MA: Market authorization

MDSTC: Manitoba Drug Standards and Therapeutics Committee

MPS: Mucopolysaccharidosis

N-ATP: National Average Transaction Price

NDS: New Drug Submission

NIH: National Institutes of Health

NOC: Notice of Compliance

NORD: National Organization for Rare Disorders

NPC: Niemann-Pick Type C

ODA: *Orphan Drug Act*

ODB: Ontario Drug Benefit

OOGP: Open Operating Grant Program

PBDP: Provincial Borders Drug Program

pCODR: pan-Canadian Oncology Drug Review

pCPA: pan-Canadian Pharmaceutical Alliance

PLA: Product Listing Agreements

PM(NOC): *Patented Medicines (Notice of Compliance) Regulations*

PNH: Paroxysmal Nocturnal Hemoglobinuria

QALY: Quality-adjusted life-year

RAMQ: Régie d'assurance maladie du Québec

R&D: Research and development

REB: Research Ethics Board

Review Panel: Expert Committee on Drug Evaluation and Therapeutics

RQMO: Regroupement québécois pour les maladies orphelines

SAP: Special Access Programme

SAR: Special Access Request

SSNDS: Supplement to a New Drug Submission

TS: Tourette's syndrome

UHN: University Health Network

UMA: utilization management agreement

US: United States

Glossary

Adverse event: Any undesirable experience associated with the use of a medical product in a patient.

Biomarkers: A measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure.

Chelation process: A type of bonding of ions and molecules to metal ions.

Cryopyrin-Associated Periodic Syndrome: A group of rare, inherited, autoinflammatory diseases with the same genetic basis and overlapping symptomatology.

Enzyme replacement therapy: A generic term for therapeutic administration of a congenitally defectiveor absent enzyme, which may be adminstered: directly, by coupling the enzyme to a carrier molecule or by organ transplantation; or indirectly, by introducing the gene into the recipient.

Fabry disease: A rare genetic disease; it is an X-linked lysosomal storage disorder caused by the deficiency of the alpha-Galactosidase A enzyme leading to accumulation of glycosphingolipids in biological fluids, organs and the vascular endothelium.

Gaucher Disease: A rare, inherited metabolic disorder in which deficiency of the enzyme glucocerebrosidase results in the accumulation of harmful quantities of certain fats (lipids), specifically the glycolipid glucocerebroside, throughout the body especially within the bone marrow, spleen and liver. The symptoms and physical findings vary greatly from patient to patient.

Genome: The complete set of genes or genetic material present in a cell or organism.

Genotype: The genetic constitution of an individual.

Health Technology Assessment procedures: The systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision-making.

Lysosomal storage disorders: are inherited metabolic diseases that are characterized by an abnormal build-up of various toxic materials in the lysosomes of body's cells as a result of enzyme deficiencies.

Mucopolysaccharidosis: Any of a group of inherited metabolic disorders in which mucopolysaccharides accumulate in various tissues, often leading to skeletal abnormalities, mental retardation, and reduced life expectancy. These conditions are also referred to by their original names, which are Hurler, Hurler-Scheie, Scheie (all MPS I),

Hunter (MPS II), Sanfilippo (MPS III), Morquio (MPS IV), Maroteaux-Lamy (MPS VI), Sly (MPS VII), and Hyaluronidase deficiency (MPS IX).

Niemann-Pick type C disease: A type of Niemann-Pick disease inherited in an autosomal recessive manner, resulting in lipid storage in the brain and body. At the cellular level, the disorder is characterized by the accumulation of cholesterol and glycolipid. Most (about 95%) of patients have mutations in the NPC1 gene in chromosome 18q11, which encodes a large membrane glycoprotein.

Pharmacoeconomics: the branch of economics that uses cost-benefit, cost-effectiveness, cost-minimization, cost-of-illness and cost-utility analyses to compare pharmaceutical products and treatment strategies.

Pharmacokinetics: the branch of pharmacology concerned with the movement of drugs within the body.

Phenotype: The physical and/or biochemical characteristics of a person, an animal or other organism, which are determined by their genetic make-up and/or environment.

Pompe Disease: a rare multisystem genetic disorder that is characterized by absence or deficiency of the lysosomal enzyme alpha-glucosidase. This enzyme is required to breakdown (metabolize) the complex carbohydrate glycogen and convert it into the simple glucose sugar.

Prevalence: The proportion of a whole population affected by a certain condition.

Quality-adjusted life year (QALY): A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.

Side effects: A secondary, typically undesirable effect of a drug or medical treatment.

Statistical power analysis: Statistical power is the likelihood that a study will detect an effect when there is an effect there to be detected. Statistical power is affected chiefly by the size of the effect and the size of the sample used to detect it. In general, the larger the sample size, the higher statistical power in the analysis.

Introduction

There is still ongoing debate over how to define "rare" or "orphan" diseases, and the "orphan" drugs often used to treat them.

So, how to define "rare" or "orphan" diseases?

In the Oxford Dictionary, the term "rare" refers to an event, a situation or condition not occurring very often, and provides the following example: a rare genetic disorder[1]. The definition or the word "rare" has been the subject of conflicting debate, as early as in the 1970s. The word "rare" - as in the rarity of a disorder - was used by doctors up until the late 1960s as an attribute of a complex diagnosis, such as a rare localization of a condition, a rare form of a disease, a rare cause of a disease, a rare complication or simply an unusual case report. In fact, it was used by clinicians to refer to a specific organ disease, such as a "rare kidney disease" or a "rare brain disorder"[2]. It is worth clarifying that this work will not examine "neglected diseases", a group of communicable diseases which prevail in tropical and subtropical nations, but can also be occasionally found in developed countries, such as Canada and the United States (US) (i.e. Dengue fever, malaria)[3].

A recent sociological approach reports that in the 1980s, in order to better understand rare diseases, the views of different groups of individuals had to be taken into account: patients, physicians, public bodies and the pharmaceutical industry[4]. The

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[1] "rare – definition of rare in English from the Oxford dictionary", online: <http://www.oxforddictionaries.com/definition/english/>

[2] Caroline Huyard, "How did uncommon disorders become 'rare diseases'? History of a boundary object", (2009) 31:4 Sociology of Health & Illness 463. doi: 10.1111/j.1467-9566.2008.01143.x

[3] World Health Organization, online: <www.who.int/neglected_diseases/diseases/en> (Accessed April 3 2016).

[4] Huyard, *supra* note 2 at 465.

author alleged that rare diseases are "a meaningless category for physicians, it relates to the patients' experience of illness, whereas the pharmaceutical industry first considered it as being synonymous with small markets, and then with innovation. Public bodies contributed to framing a common and blurred use, based on a statistical definition whose purpose was to foster cooperation between the four groups involved in the issue"[5].

The term "rare" diseases and the category of rare diseases seem to have surfaced in the United States in the mid-1970s subsequent to the orphan drug issue, a consequence of the Kefauver-Harris Amendments in 1962 to the Food, Drug and Cosmetic Act of 1938[6].

These amendments insisting on proof of the effectiveness, safety and reliability of drugs available since 1938 in the United States were necessary following the thalidomide tragedy, and also, in order to protect the health of the public[7]. Therefore, drugs had to be reviewed to meet the criteria of the new legislation to be approved, or be taken off the market[8]. These 1962 amendments were part of a major restructuring of the approval process for drugs in the United States, but they also affected the development of drugs and the ongoing process of alterations of the policies regulating the industry[9]. In fact, the Drug Efficacy Study Implementation program created by the Food and Drug Administration (FDA) in 1962 reviewed and re-evaluated the effectiveness of drug products, which resulted in the removal of more than 1000 medicines that were on the

[5] *Ibid*.
[6] *Drug Amendments Act of 1962*, Public Law No 87-78, 76 Stat 780.
[7] Jeremy A Greene & Scott H Podolsky, "Reform, Regulation, and Pharmaceuticals — The Kefauver–Harris Amendments at 50" (2012) 367:16 New England Journal of Medicine at 1482.
[8] *Drug Amendments Act of 1962*, *supra* note 6.
[9] Carolyn H. Asbury, *Orphan Drugs:medical versus market value* (Lexington, Mass: Lexington Books, 1985), at 21.

market[10]. Different aspects of drug efficacy and safety were evaluated "through provisions affecting drug testing and approval, labeling, advertising and monitoring of firms"[11]. Moreover, a Library of Congress study approved by Kefauver evaluated 34 trade-named drugs extensively used by physicians and advertised in scientific medical journals between July 1958 and March 1959. This study revealed that 89% of these advertisements did not indicate or had minimal indications of adverse effects[12]. This situation was troubling for physicians prescribing these drugs, since it meant they might not have had the adequate information for their patients.

Although certain drugs were taken off the market for their inefficacy, some of them were neither reviewed nor withdrawn. In fact, hospital pharmacies were becoming part of a major concern because of their usage of non-approved substances, which had no label for drug indication. Some of these chemical substances used in hospital pharmacies would have been commercially unprofitable through a New Drug Application and therefore, were labeled as "manufacturing use only", "for chemical purposes", "for research use only, not for clinical use", or "for investigational use only, not for drug use"[13]. Researchers coined the term "homeless" or "orphan" drugs to refer to substances whose usage was not approved or labeled as a drug and so, metaphorically speaking, they had no home[14].

Some examples of orphan drugs at that time were the corticosteroid ACTH (Adreno Cortico Trophic Hormone) for multiple sclerosis, pentamidine for the treatment

[10] Office of the Commissioner, "Overviews on FDA History - FDA and Clinical Drug Trials: A Short History",online:<http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm>(Accessed April 12 2016); See also *supra* note 7.
[11] Asbury*, supra* note 9 at 21
[12] *Ibid* at 23.
[13] George P. Provost,"Homeless' or 'orphan' drugs" (1968) 25:11 Am J Hosp Pharm 609.
[14] *Ibid*.

of a rare form of pneumonia and the development of anticancer agents by the National Cancer Institute[15]. The major issue with orphan drugs for rare diseases in the '80s, and even before, was that, although medically important, they were found to be unprofitable by the pharmaceutical industry.

Nevertheless, in some cases, lone individuals were successful in bringing a drug to market for treating patients affected with rare diseases. The 1956 story of J.M. Walshe, a neurologist, merits attention. He introduced one drug called penicillamine to treat Wilson's disease, an autosomal recessive rare disorder leading to the accumulation of copper in tissues and severe clinical manifestations[16] (it was later introduced for other diseases as well). Briefly, penicillamine binds to copper as part of a chelation process followed by copper excretion in urine. The drug is efficient for treating the disease, but there is a possibility of a toxic effect when administered to patients over the long term. Therefore, Walshe decided to introduce a new oral drug in 1966 called triethylene tetramine dihydrochloride, which was a copper-chelating compound. Since this drug was not supported or manufactured by the pharma industry, he had to produce it in his own laboratory without any toxicity studies. However, his efforts led to a medication that saved the lives of those affected with this rare disease[17].

In 1983, the term "rare diseases" was officially adopted by the *Orphan Drug Act* (ODA)[18]. Rare diseases or orphan diseases are often interchangeable terms but the core of the definition is important, even though there is no consensual definition at the moment. The usage and the definition of the term are relevant when it comes to the

[15] Asbury*, supra* note 9.
[16] J.M. "Letter: Drugs for rare diseases" (1975) 3:5985 Br Med. J. 701.
[17] Anon. Drugs for rare diseases, (1976) The Lancet, 2, 7990, 835–6.
[18] *Orphan Drug Act*, Pub L. No. 97-414, 96 Stat 2049 (1983).

designation of a particular drug and its policies, especially, when introducing new legislation.

An estimate of 7,000[19] to 8,000 rare diseases have been recognized affecting altogether 6-8% of the general population[20]. It should be emphasized that even if they are called "rare or orphan diseases", the clinical manifestations can be severe, in some cases leading to the death of the affected individuals[21]. These diseases are found in significant numbers (75%) in newborns and children[22]. Some are detected early through neonatal screening, while others are detected later on in life[23]. Eighty percent of rare diseases are of genetic origin[24]. A marked heterogeneity in the phenotype and genotype of most rare diseases increases the complexity of monitoring, management and follow-up of affected patients. According to the Canadian Organization for Rare Disorders (CORD), the number of persons affected with a rare disease in Canada is estimated at 1 in 12, or approximately 3 million Canadians[25]. This gives the impression that, when all these diseases are taken together, the descriptor no longer seems appropriate and therefore, these diseases are not so rare after all.

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[19] "About CORD | Canadian Organization for Rare Disorders", online: <https://www.raredisorders.ca/about-cord/>. > (Accessed April 12 2016).

[20] Domenica Taruscio, Linda Agresta & Et Al, "The Italian National Centre for Rare Diseases: where research and public health translate into action" Blood Transfusion (2014) 12 Suppl 3: s591-605 doi 10.2450/2014.0040-14s.

[21] Wim Pinxten et al, "A fair share for the orphans: ethical guidelines for a fair distribution of resources within the bounds of the 10-year-old European Orphan Drug Regulation" (2012) 38:3 J Med Ethics 148.

[22] "EURODIS What is a rare disease? - Rare Diseases Europe", 2015, online: <http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf> (Accessed 7 April 2016.)

[23] "MSSS - Sujets - Santé publique - Dépistage néonatal - Sanguin et urinaire - Description et admissibilité", online: <http://www.msss.gouv.qc.ca/sujets/santepub/depistage-neonatal/>. (Accessed 10 March 2016).

[24] "About Rare Diseases | www.eurordis.org", online: <http://www.eurordis.org/about-rare-diseases>. (Accessed May 21 2016).

[25] "Canada's Rare Disease Strategy | Canadian Organization for Rare Disorders", online: <https://www.raredisorders.ca/canadas-rare-disease-strategy/>. (Accessed April 12 2016).

However, there are different groups of rare disorders, such as autoimmune diseases, infectious diseases, genetic diseases, rare cancers, congenital malformations, and sometimes, diseases of unknown nature[26]. An alphabetical list of rare diseases is available from Orphanet[27]. Orphanet is the "reference portal" designed to provide specific information on rare diseases to affected patients, as well as caregivers[28]. This list provides at a glance the disparity of diseases ranging from Acheiria (a congenital disease characterized by the absence of one or both hands) to Progeria (also known as Hutchinson-Gilford syndrome, a genetic condition characterized by dramatic aging in childhood). It also offers the latest news and developments on orphan drugs. Orphanet is comprised of a consortium of 40 countries working together under the coordinating endeavor of the "Institut national de la santé et de la recherche médicale" (INSERM) in France[29]. The main objective of the Orphanet consortium is to improve the diagnosis, monitoring, treatment and overall care of patients with rare diseases.

Even if Orphanet maintains an updated survey of the scientific literature to estimate the prevalence (the proportion of the population that has any given disease at a specific point in time) and incidence (it measures the rate of occurrence of new cases of a disease or condition in a particular population in a specific time period) of rare

[26] Stéphanie Elger et al, *Prise en charge des maladies rares expériences étrangères: rapport* (Québec: Institut national d'excellence en santé et en services sociaux, Québec, 2011).

[27] Orphanet Report Series - List of rare diseases and synonyms listed in alphabetical order - March 2016 online: <http://www.orpha.net/orphacom/cahiers/docs/GB/List_of_rare_diseases_in_alphabetical_order.pdf> (Accessed 14 April 2016).

[28] "Orphanet: About Orphanet", online: <http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN>.(Accessed 14 April 2016).

[29] INSERM: it is a public scientific and technological body operating in France and oriented towards medical research. It is under the Ministry of Research and the Ministry of Health, online: "Inserm – French National Institute of Health and Medical Research", online: < http://english.inserm.fr/> (Accessed 14 April 2016).

diseases[30], surprisingly, there is no real consensus about the definition of a rare disease in terms of the number of patients affected. In the United States, according to the "*U.S Orphan Drug Act",* a rare disease is one that affects less than one individual per 200,000[31]. In the European Union, "*The European Orphan Drug* Regulation" states that it is 1 in 2000[32]. In 2014, Health Canada, through its then-Minister of Health, Rona Ambrose, stipulated the following definition for orphan drugs, rare diseases, and the frequency of a rare disease (which is similar to the frequency established by the European Union):

> Orphan drugs are those drugs used to treat rare diseases. A rare disease is a life-threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons)[33].

A few years earlier, in 2012, another definition of rare diseases was presented during a press conference by Leona Aglukkaq, then-Minister of Health. It offers somewhat more information regarding the definition of a rare disease:

> A rare disease is a life-threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients. It's estimated that there over 7,000 unique rare disorders, many of which are genetic. While some of these rare disorders may affect only a handful of Canadians, in all, hundreds of thousands of Canadians are dealing with these conditions and need effective

[30] Orphanet - Prevalence, incidence or reported number of published cases listed in alphabetical order of disease March 2016 - n°1, online: <http://www.orpha.net/orphacom/cahiers/docs/GB /Prevalence _of_rare_diseases _by_alphabetical_list.pdf > (Accessed 14 April 2016)
[31] *Orphan Drug Act, supra* note 18.
[32] "European Medicines Agency - Human regulatory - Orphan designation", May 22 2013 online: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce>.(Accessed 14 April 2016)
[33] Health Canada Government of Canada, "Canada News Centre - Archived - Minister Ambrose Announces Patient Involvement Pilot for Orphan Drugs", (August 6, 2014), online: <http://news.gc.ca/web/article-en.do?nid=873619>.(Accessed 12 March 2016)

> treatments. Drugs used to treat rare diseases are often referred to as orphan drugs[34].

One major issue faced in rare disease research studies is the fact that it is often quite difficult to find a sufficiently large number of patients to participate in clinical trials. Without a powerful statistical analysis, agencies such as Health Canada have little on which to guide the decision whether to authorize an orphan drug[35]. Some solutions have been proposed[36], but still, governmental agencies, such as Health Canada, are reluctant to accept orphan drugs without large cohorts of patients.

Another issue is the major financial investment necessary on the part of pharmaceutical companies for drug development for rare disorders until it reaches the final marketing process[37]. There are thus major pharmacoeconomic issues to overcome before an orphan drug reaches market.

Rare diseases have become somewhat of a legal and political quandary. Patients affected with rare diseases have advocated their needs, which have consequently generated major concerns throughout the media for quite some time now, especially regarding drug reimbursement. The decision-making for reimbursing drugs in Canada is based mainly on the efficacy of the drug, its cost, and on the quality-adjusted life-year (QALY).

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[34] A statement by the Minister of Health in Canada, Leona Aglukkaq, in 2012, Health Canada Government of Canada, "Canada News Centre - Archived - Harper Government Takes Action to Help Canadians with Rare Diseases - Launch of First Ever Canadian Framework to Increase Access to New Treatments and Information and Orphanet-Canada Online Portal", (3 October 2012), online: <http://news.gc.ca/web/article-en.do?nid=698449>.(Accessed 15 April 2016)

[35] Joe TR Clarke et al, "Toward a Functional Definition of a "Rare Disease" for Regulatory Authorities and Funding Agencies" (2014) 17:8 Value in Health 757.

[36] Mohamed Amine Bayar et al, "New insights into the evaluation of randomized controlled trials for rare diseases over a long-term research horizon: a simulation study: A new strategy for clinical trial design in rare diseases" (2016) Statistics in Medicine. doi: 10.1002/sim.6942

[37] Evaluate Pharma Orphan Drug Report 2015, 3rd Edition-October 2015.

Moreover, there is an important need to move towards personalized medicine, and access to new drugs where patients may substantially benefit. With the advancement of technology, it is now possible to use genomic applications in daily clinical practice[38]. Patients affected with the same rare disease might have a variable genotype necessitating a different treatment approach, a different dose of an orphan drug, at a different frequency. This might affect the cost of the lifelong treatment for these life-threatening diseases.

The main objective of this thesis will be to evaluate some of the difficulties regarding the legal and policy framework, considering the fact that there is no orphan drug legislation in Canada. Possible solutions, as well as recommendations, will be proposed for a policy framework for orphan drugs. In order to attain this goal, a thorough evaluation of the current framework at the federal and provincial levels will be evaluated, as well as the legal situation in the United States and European communities.

1. Legal and Policy Challenges Relating to Orphan Drugs in Canada

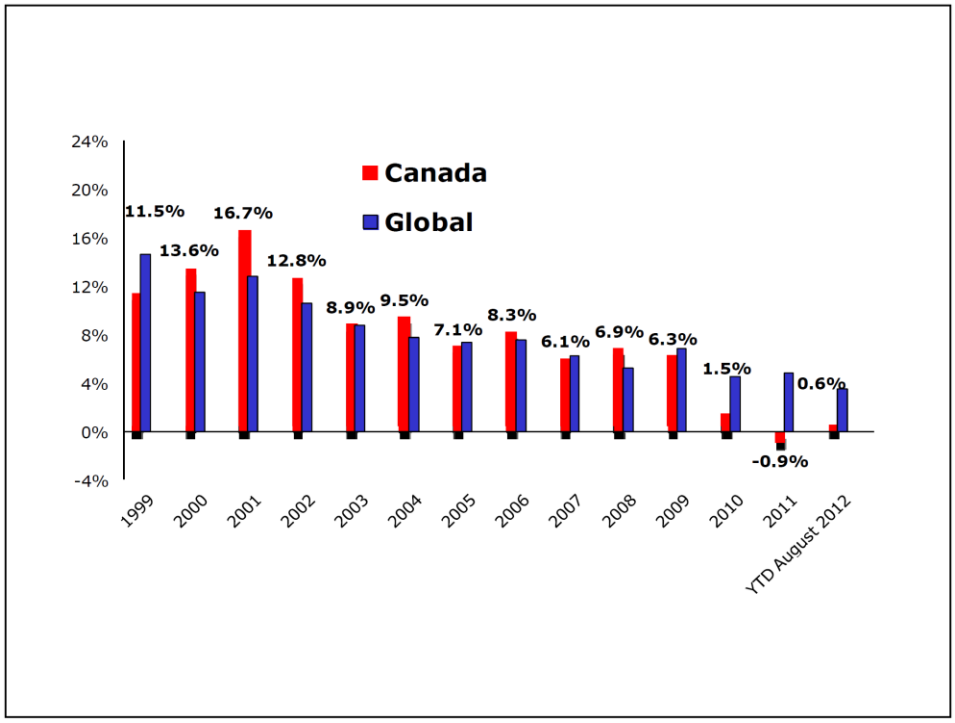
Recent statistics about the overall pharmaceutical market performance in Canada in comparison with global growth revealed astounding negative data (Figure 1)[39]. In fact, the decline in the performance is problematic reaching a low of -0.9% in 2011, and just barely above the positive rate (0.5%) in 2012. Different reasons have been suggested to account for this lagging growth in the performance of the pharmaceutical Canadian market:

[38] Casey Lynnette Overby, et al., Opportunities for genomic clinical decision support interventions, Genet Med. 2013 October ; 15(10) doi:10.1038/gim.2013.128.

[39] Innovation Government of Canada, "Canada's Pharmaceutical Industry and Prospects", IMS Brogan, 2016, online: <https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/hn01768.html>. (Accessed 15 May 2016).

For the most part, the factors contributing to the slowdown in Canadian market growth since the second half of the past decade have also been responsible for dampening growth in other developed markets and the overall global rate. These factors include: record levels of loss of exclusivity for major brand products, a lack of new blockbuster products, sluggish uptake of new products, a slowdown in new product approvals and longer processing time to access public formularies. More recently, these market factors have been compounded in Canada and other global markets by declining R&D productivity, the global financial crisis and economic downturn, downward pressure on prices and cost containment policies from payers, and the shift in business operations towards emerging countries[40].

Figure 1. Comparison between Overall Global and Canadian Pharmaceutical Market Performance



Source: Pharmafocus 2016, IMS Brogan

[40] *Ibid.*

Why has Canada lowered its R&D productivity over the last few years? Research and development productivity in the pharmaceutical industry is a key factor assuring growth, development and innovation. The importance of research and development in the pharmaceutical field, and in particular in orphan drugs for rare diseases, is equivalent to long-term success for a company[41], but it also improves the lives of patients who will benefit from these drugs. In addition, there are still issues to overcome:

> Delineating the general value of multiplier effect of research on specific rare diseases is important because such research may otherwise be undervalued when policy makers consider the absolute numbers of people likely to benefit from a particular public investment in research[42].

Unfortunately, Canada has seen a decline in its endeavours in the pharmaceutical field affecting a major part of its economy. The commitment of the government towards research and development (R&D) policies focusing on academia should thus be prioritized.

1.1 At the Federal Level

1.1.1. Research Stage: a Major Hurdle to Obtain Funds for Rare Diseases

As mentioned above, the research stage is one of the most important and often the most complex step in the development of a new drug. It involves academic, as well as industry-related research. For pharmaceutical companies, it involves a large capital investment, which has been estimated at billions of dollars over decades of research and

[41] Mark Howard, The Importance of Continued Investment in R&D, Pharmaceutical Technology, Volume 37, Issue 9, Sep 2013. Online: <http://www.pharmtech.com/importance-continued-investment-rd> (Accessed May 20 2016).
[42] Marilyn J Field et al, eds, *Rare diseases and orphan products: accelerating research and development* (Washington, DC: National Academies Press, 2010) at 16.

the development of complex processes for drugs to reach the market[43]. More than 1,673 planned, ongoing or completed research studies on rare diseases have been reported around the world in 2015[44]. There is lack of information on the etiology and pathophysiology of many rare diseases. Unfortunately, knowledge about the natural history of diseases has often been missing over the years. In fact, natural history of diseases is a key factor in understanding how different diseases progress in patients without treatment starting from the presymptomatic phase until the final outcome of the disease. Therefore, data collection during natural history studies will provide longitudinal information and support product development and their eventual approval. Nonetheless, a paradigm shift has recently occurred favouring the understanding of these rare diseases:

> Knowledge from these studies is essential for the development of research hypotheses, identification of potential biomarkers, and phenotype variations in patients. Due to the high cost of initiating and maintaining studies for many years, there has been a reluctance to support these studies. Only in recent years has the values of these studies been accepted by the research community as a generator of new research hypotheses and information for research and treatment for rare diseases[45].

There is a tremendous need for financial support for orphan diseases research. Canada is part of the "International Rare Diseases Research Consortium (IRDiRC)", a group devised by the European Commission and the National Institutes of Health (NIH) in 2011[46]. It focuses on international collaborative research aiming to hasten the

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[43] *Supra* note 37.

[44] "Clinicaltrials.gov, - A Service of the US National Institutes of Health", online: <https://clinicaltrials.gov/> (Accessed April 15 2015).

[45]Manuel Posada de la Paz & Stephen C Groft, *Rare Diseases Epidemiology*, Advances in Experimental Medicine and Biology, vol. 686 (Dordrecht: Springer Netherlands, 2010) at 8 doi:10.1007/978-90-481-9485-8

[46] "Governance Structure & Members", (16 January 2013), online: *IRDiRC*

development of diagnostic tools and therapies for orphan diseases. This consortium is comprised of "regulatory agencies, researchers, patient group representatives, members of the biopharmaceutical industry, and health professionals" [47]. Members of the consortium are working together to share information and facilitate networking for researchers to better understand the pathophysiology of these diseases, develop specific models which can be useful in drug discovery, evaluate the response to treatment by the discovery of novel biomarkers, and support the registries of patients. However, it is not a funding agency, but it is a facilitator for international research endeavour in rare diseases[48].

In Canada, the availability of research funding for rare diseases for biomarker discovery, for detection, diagnosis, monitoring the efficacy and safety of treatment is a major issue. Patients affected with rare diseases are often unaware of the difficulties encountered to better understand the fundamental basis of a rare disease. Canadian governmental funding bodies often prioritize their research funds to common diseases considering the public health issues involved due to the high number of affected individuals (e.g. Diabetes mellitus type 2). Therefore, a researcher requesting funding for rare diseases through the Canadian Institutes of Health Research (CIHR) open-grant applications will definitely be disadvantaged considering the small population affected

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<http://www.irdirc.org/governance-structure-members/>; Chris Wilson, "Policies and research funding" in *Orphan Drugs* (Elsevier, 2013) at 179. doi:10.1533/9781908818393.145

[47] *Ibid* at 180.

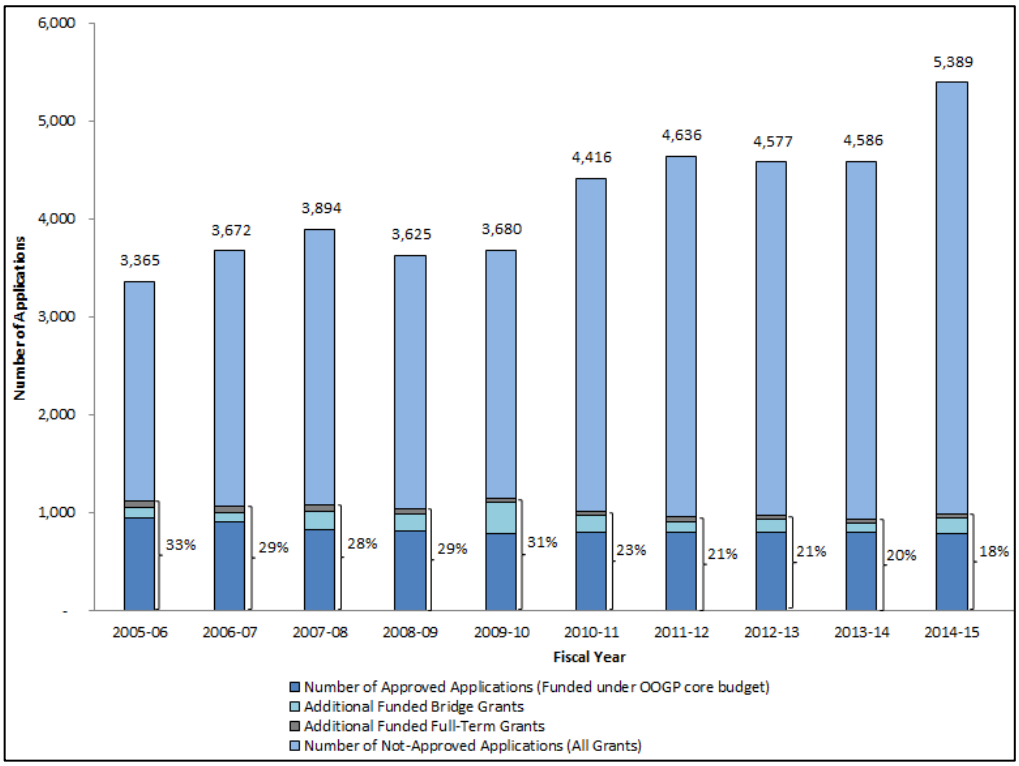
[48] *Ibid* at 180. Also in: Aymé S, Lau L, Peixoto S, Unni D, Höhn S, Mills A, Eds., "State of Play of Research in the Field of Rare Diseases: 2014- 2015", September 2015 at 4, online: <http://www.irdirc.org/wp-content/uploads/2015/09/IRDiRC_State-of-Play-2015.pdf> (Accessed April 10 2015). This latter report "aims to inform stakeholders at large of developments in the field of rare diseases research in order to support decisions of policy makers and research funders, as well as informed the rare diseases community at large of the achievements and of observed trends which shape the future of research and development for rare diseases".

with rare diseases[49]. In order to achieve statistical power analysis, and to draw adequate research conclusions, there needs to be a satisfactory number of patients recruited in translational and clinical research projects. These patients are often difficult to recruit because they are so few of them. These are some of the reasons why the natural history of specific rare diseases is still unknown. There is thus a definite need to increase research funding for rare diseases in Canada. As shown in Figure 2, funding statistics from the CIHR from 2005 to 2015 reveals that the percentage of grant approvals in the Open Operating Grant Program (OOGP) has been lowered from 23% to 18% for years 2010-2015[50]. The OOGP supports all areas of health research proposals, including randomized controlled trials. Research studies on rare diseases and orphan drug proposals fall within this program[51].

This graph also confirms a definite lowering trend for funding R&D, including rare diseases. There is thus a clear need to convince the political authorities to provide increased research funds for governmental bodies in Canada, in the specific "orphan disease field".

[49] Samir Gupta, "Rare diseases: Canada's 'research orphans'" (2012) 6:1 Open Med e23.
[50] Canadian Institutes of Health Research Government of Canada, "ARCHIVED – CIHR Open Operating Grant Program Competitions – Frequently Asked Questions (FAQ) – 2014 - CIHR", (21 February 2014), online: <http://www.cihr-irsc.gc.ca/e/47960.html>. (Accessed April 2 2016).
[51] Applying to CIHR's Open Operating Grant Program (OOGP) at Western University online: <https://www.uwo.ca/research/_docs/resources/CIHR_OOGP_Guidebook_Winter_2015.pdf>. (Accessed June 1 2016).

Figure 2. Application and Funding Statistics for the Open Operating Grant Program and Other Related Programs



Source: Canadian Institutes of Health Research 2014

Among other possibilities to obtain research funds for rare diseases, the approval of an Investigator Initiated Research (IIR) grant from the pharmaceutical industry can be matched with CIHR funds as part of an Operating Grant: Industry-Partnered Collaborative Research program, meaning increased financial support for R&D. This program was still in effect as of 2015[52]. However, with this program, difficulties lie in the fact that, researchers must first convince the pharma industry of the feasibility and novelty of their proposal in order to obtain funds, and in the second phase, convince the

[52] Canadian Institutes of Health Research Government of Canada, "CIHR and its partners announce the June 2015 Funding Opportunities and Priority Announcements - CIHR", (24 June 2015), online: <http://www.cihr-irsc.gc.ca/e/49215.html> (Accessed April 3 2016) and for more information at Canadian Institutes of Health Research Government of Canada, "Commercialization of Research - CIHR", (16 April 2012), online: <http://www.cihr-irsc.gc.ca/e/44911.html>. (Accessed April 3 2016).

governmental body to accept the proposal. It is a long, cumbersome, and tedious process for researchers.

Nevertheless, this expanding role of academic centres in R&D for rare diseases has led to novel partnerships with the pharma industry[53] allowing innovative research to be pursued. Direct financial research support may also be requested from the pharmaceutical/biotechnology companies. If approved by the company, an agreement stating all legal considerations such as intellectual property, timelines, publication rights, ownership of data, etc. has to be signed by all the parties. It should be emphasized that this pharmaceutical funding opportunity remains dependent on the views and long-term vision of companies regarding research themes, investment strategies, and desire to work with academia.

1.1.2. Clinical Trials

Clinical trials are major steps in the process of drug approval and are crucial in verifying efficacy and safety. Once a drug discovery is confirmed by a laboratory, it may typically take up to 12 years before the drug is approved and marketed in Canada until it reaches patients' needs [54].

Before clinical trials begin, there is always an evaluation of the return on investment on the part of pharmaceutical companies when they decide to invest in the manufacturing of orphan drugs. Statistics have shown that the expected return on investment of Phase III clinical trials for filed orphan drugs has been evaluated at 1.14

[53] David C Pryde & Michael Palmer, eds, *Orphan Drugs and Rare Diseases*, RSC Drug Discovery (Cambridge: Royal Society of Chemistry, 2014) at 26.
[54] "Phases of Development | Pfizer: One of the world's premier biopharmaceutical companies", online: <http://www.pfizer.com/research/clinical_trials/phases_of_development>. (Accessed April 3 2016).

times greater than non-orphan drugs. The main difference for this return on investment is due to the clinical trial size. In fact, all phase III clinical trials in 2015 required 44,357 patients for orphan drugs, whereas it required 426,951 patients for non-orphan drugs[55].

In general, there are specific requirements to efficiently conduct a clinical trial. The first basic criterion is that the medical question, which needs to be addressed, is valuable and significant for patients. Secondly, the clinical trial must rely on a methodology respecting comprehensive and rigorous principles and practice guidelines[56], which address the medical question, and thirdly, the ethical aspects for clinical research must be respected, in particular for the proportionality of risks and benefits[57].

In Canada, clinical trials are carried out according to the *Food and Drug Regulations*[58] with provision of Good Clinical Practices[59]. These latter regulations emphasize the importance of assuring the protection, the safety and well-being of persons participating in clinical trials under strict ethical conditions approved by Research Ethics Board (REB), under the Declaration of Helsinki[60] and the Tri-Council

[55] *Supra* note 37.
[56] Health Canada Government of Canada, "Guidance for Industry: Good Clinical Practice: Consolidated Guideline: ICH Topic E6", (19 September 1997), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php>. (Accessed April 4 2016)
[57] *Ibid*, note 45, at 174.
[58] *Food and Drug Regulations,* C.R.C., ch. 870, s. C.05.010.
[59] Mathieu Gagné, *Précis de droit pharmaceutique* (Cowansville, Québec: Éditions Y. Blais, 2012) at 50.
[60] "WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects", (19 October 2013), online: <http://www.wma.net/en/30publications/10policies/b3/>.(Accessed April 4 2016)

Policy statement in Canada[61]. The sponsor always needs to obtain REB approval before the start of the clinical trial.

1.1.2.1 Low Number of Rare Disease Patients for Clinical Trials

Clinical trials in rare diseases raise the key question of the limited number of patients affected with a particular disease who can participate in a given trial. This issue may affect the second aforementioned goal to use a methodology that respects rigorous principles, such as statistical power analysis. The design of the trial must therefore rely on alternative statistical approaches[62]. One approach concerns the "risk-based allocation designs" when a randomized trial is not possible. This approach may be a solution for a clinical trial designed to evaluate two dosages (high and low concentrations) of an orphan drug provided to a group of patients having heterogeneous clinical manifestations ranging from an attenuated form (low-risk) to a severe form (high-risk) of the disease. Low-risk patients will be randomized in two groups: one will receive the high dosage and the other the low dosage, whereas high-risk patients will receive only the high dosage of the drug. Standard statistical analyses will be performed for the low-risk patients. These data will help establish a risk-responsive model, which will enable the prediction of expected additional benefits from the high dosage treatment[63]. Even so, these reduced sample groups designed for rare disease clinical trials for drug approval might not be accepted by Health Canada.

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[61] Medical Research Council (Canada), Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humananities Research Council of Canada, *Tri-council policy statement ethical conduct for research involving humans 2014* (2014).
[62] *Supra* note 45 at 174.
[63] *Ibid* at 184.

In 2012, a comparison between clinical trials in rare diseases (n=2,759) and non-rare diseases (n=21,329) has revealed major differences between the two groups by analyzing data from the Aggregate Analysis of ClinicalTrials.gov (AACT) database[64]. In this study, the results show 83 Canadian rare disease trials and 1,357 non-rare disease trials during that particular period. The main differences between these two trial groups, e.g. rare diseases and non-rare diseases, in the overall study were in the characteristics in the design of the study where a lower percentage of rare disease trials are done in a single centre (61.3%) *versus* non-rare disease trials (72.7%). This is understandable considering the difficulty in recruiting rare disease patients in a single centre. It seems that clinical trials for rare diseases are mostly phase 1 and phase 2 trials with a high percentage of 72.5% compared to 38.5% for non-rare disease trials[65]. There are more studies for early phase I and II clinical trials for rare diseases because they require knowledge about drug pharmacokinetics, efficacy, side effects and risk before going further with phase III trials. The main goal of rare disease trials is oriented towards treatment evaluation in 91.2% of the studies compared to 79.3% in non-rare disease trials. Moreover, the evaluation of drug intervention is more common in 79.9% of rare-

[64] Stuart A Bell & Catrin Tudur Smith, "A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov" (2014) 9:1 Orphanet Journal of Rare Diseases, online: <http://ojrd.biomedcentral.com/articles/10.1186/s13023-014-0170-0>.

[65] Phase I clinical trials are designed mainly to determine the pharmacological actions of the drug and the safety (side effects) associated with increasing doses. Pharmacokinetic studies (evaluating drug levels in tissues such as blood) as well as drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development. Phase I trials are generally conducted in healthy volunteers, but may be conducted in patients when administration of the drug to healthy volunteers is not ethical. Phase II clinical trials evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with the drug. If a new indication for a marketed drug is to be investigated, then those clinical trials may generally be considered Phase II trials. These trials provide preliminary information on the safety and efficacy of the drug in patients. Health Canada Government of Canada, "Glossary - Health Canada's Clinical Trials Database", (29 May 2013), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/terminolog-eng.php>. (Accessed June 1 2016)

disease trials *versus* 55.8% in non-rare diseases. Patients affected with rare diseases need specific clinical trials for treatment evaluation as well as drug intervention since both are often lacking.

Rare disease trials often have more single group assignment (63%) than non-rare diseases (49%). Moreover, rare disease trials rely on non-randomization in 64.5% *versus* 28.4% in non-rare disease trials. The single group assignment and non-randomization of clinical trials are mostly resulting from smaller sample size cohorts of rare disease patients available for these trials. Open label clinical trials refer to the evaluation of a new drug or treatment where both patients and physicians are aware of the type of drug received and treatment given. Open label is more frequent in rare-disease trials at 78.7% *versus* 52.2%, considering that often, there are no other alternative treatments and that open label trial can provide information regarding drug safety. Rare disease trials are also more likely to explore both safety and efficacy endpoints in the same trial in 63.2% compared to non-rare disease trials in 45.9%, considering the smaller pool of rare diseases patients available compared to non-rare diseases patients. In conclusion, this recent study shows major differences in both rare-disease trials and non-rare disease trials, in particular in regards to blinding and randomization, which are considered as state-of-the art procedures in clinical trials, and which are less used in rare-disease studies. This may lead to lower quality design trials, and to concerns about the evidence-based information provided by these trials, as well as the possibility of random errors[66].

[66] *Supra* note 64.

1.1.3 Existing Canadian Regulations and Policies for Drugs

Orphan drugs in Canada fall under the *Food and Drug Act*[67] and the associated *Food and Drug Regulations*[68], and follow the same approval and marketing authorization as any other medication provided for widespread diseases such as diabetes, hypertension and hypercholesterolemia. In other words, every drug marketed for treatment or prevention of diseases and symptoms in Canada must be approved by Health Canada[69]. In order to be approved, the innovator must file a "New Drug Submission" (NDS) or a "Supplement to a New Drug Submission" (SNDS), followed by registration, if appropriate, to be on a patent list according to the *Patented Medicines (Notice of Compliance) Regulations* or "PM(NOC)"[70]. The Patent Register consists of an alphabetical list of patents and their associated medicinal ingredients, as well as the patent expiration dates[71]. However, a drug may receive marketing authorization without the patent featured on the Patent Register for that specific drug, since the submission of the patent list is not mandatory[72]. It stands to reason that, prior to the approval, the innovator company must demonstrate the safety and efficacy of the drug by presenting exhaustive clinical trial data. The ability to approve a new drug is then subject to the discretion of Canada's Minister of Health, who will issue a Notice of Compliance

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[67] *Food and Drugs Act*, R.S.C., 1985, c. F-27
[68] *Food and Drug Regulations,* C.R.C., ch. 870.
[69] Health Canada Government of Canada, "Drug Products - Main Page - Health Canada", (26 July 2004), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index-eng.php>. (Accessed April 4 2016).
[70] *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, subsection 4(1)
[71] Health Canada Government of Canada, "Patent Register - Drug Products - Health Canada", (9 December 2002), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/patregbrev/index-eng.php>. (Accessed April 4 2016)
[72] Even though the drug cannot be found on the Patent register, the patent can be found on The Canadian Intellectual Property Office database. In order to apply for a patent, The Canadian Intellectual Property Office has the mandate to grant patents in Canada. Health Canada Government of Canada, "Frequently asked Questions: Patent Register - Drug Products - Health Canada", (13 September 2010), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/patregbrev/ptnt-faq-mbreg-eng.php>. (Accessed April 4 2016)

(NOC) to the innovator[73]. It must be noted, that according to the *Food and Drug Regulations,* a pharmaceutical company introducing a novel drug that contains new medicinal ingredients benefits from an 8-year period of exclusivity, which is extended for 6 months if information for pediatric use is provided within the first 5 years of the protection period[74]. Once the NOC is granted, it allows the drug to be marketed in Canada.

At the same time, Health Canada issues a Drug Identification Number (DIN), an eight-digit code number, which also allows the manufacturer to market the drug in Canada. In conformity with Canadian law, drug product is not permitted to be sold in Canada without a DIN. This identification number is a computer-generated code, which gives the following product characteristics: the manufacturer; product name; active ingredient(s); strength(s) of active ingredient(s); pharmaceutical form; and route of administration[75].

Reviews of drug submissions, applications or supplements to government come with associated costs, as well as DIN applications. Under the *Financial Administration Act*[76] in the 1990s, it was established that Health Canada was authorized to charge industry user fees. These fees, which included the costs of review as well as the right to sell drugs[77], aimed to recuperate the costs of service delivery for drugs and ensure "sufficient funding for Health Canada to meet service standards and support access to

[73] *Supra* note 58 s. C.08.002.
[74] *Ibid* s. C.08.004.1.
[75] DIN also includes over-the-counter drugs, Health Canada Government of Canada, "Drug Identification Number (DIN)", (8 January 2001), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/dinfs_fd-eng.php> (Accessed April 3 2016).
[76] *Financial Administration Act*, R.S.C., 1985, c. F-11
[77] *Fees in Respect of Drugs and Medical Devices Regulations* (SOR/2011-79)

drugs for Canadians in a timely manner"[78]. The fees take into account the actual gross revenue according to the sale of the drug and the costs related to the inflation rate. As of April 1st 2016, the fees for a pharmaceutical submission and application review of a New Active Substance was 335,068 Canadian dollars (Table 1)[79].

Table 1. Health Canada Pharmaceutical Submission and Application Review Fees as of April 1, 2016

Fee Category	Description	Fee as of April 1, 2015	Fee as of April 1, 2016
New Active Substance	Submissions in support of a drug , excluding a disinfectant, that contains a medicinal ingredient not previously approved in a drug in Canada and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate, or polymorph.	$328,498	$335,068
Clinical or Non-Clinical Data and Chemistry & Manufacturing	Submissions based on Clinical or Non-Clinical data and Chemistry & Manufacturing data for a drug that does not include a new active substance.	$166,383	$169,711
Clinical or Non-Clinical Data Only	Submissions based only on Clinical or Non-Clinical data for a drug that does not include a new active substance.	$77,655	$79,209
Comparative Studies	Submissions based on comparative studies (e.g. Clinical or non-clinical data, bioavailability, pharmacokinetic and pharmacodynamic data) with or without Chemistry & Manufacturing data for a drug that does not include a new active substance.	$46,937	$47,876
Chemistry & Manufacturing Data Only	Submissions based only on Chemistry & Manufacturing data for a drug that does not include a new active substance.	$22,192	$22,636
Published Data Only	Submissions based only on published clinical or non-clinical data for a drug that does not include a new active substance.	$18,402	$18,771
Switch status from prescription drug to non-prescription drug	Submissions based only on data that support the modification or removing of a medicinal ingredient listed in Schedule F of the *Food and Drug Regulations* (*i.e.* identical claim for existing drug).	$44,685	$45,579
Labelling Only	Submissions of labelling material. (i.e. does not include supporting clinical or non-clinical or Chemistry and Manufacturing data.)	$2,990	$3,050
Administrative Submission	Submissions in support of a manufacturer or product name change.	$310	$317
Disinfectants	Submissions and applications that include data in support of a disinfectant.	$4,137	$4,220
Drug Identification Number application - Labelling Standard	Applications attesting to compliance with a labelling standard or Category IV Monograph for a drug that does not include clinical or non-clinical data or chemistry and manufacturing data.	$1,658	$1,692

Source: Health Canada 2016

[78] Health Canada Government of Canada, "Guidance Document: Fees for the Review of Drug Submissions and Applications [Health Canada, 2013]", (1 May 1998), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/fees-frais/fee_frais_guide-eng.php>. (Accessed April 3 2016).

[79] Health Canada, Government of Canada, "Pharmaceutical Submission and Application Review - Funding and Fees - Drugs and Health Products - Health Canada", (1 April 2014), online: <http://www.hc-sc.gc.ca/dhp-mps/finance/fees-frais/pharma-eng.php>.

Moreover, there is a strong possibility for pharmaceutical companies to submit a new drug application in another country offering more favourable incentives. Therefore, companies will work with countries where there are more incentives.

Health Canada should have serious concerns regarding pharmaceutical companies focusing on rare diseases, since to an increasing extent, companies are looking for a unique niche in the marketplace[80]. The sales of so-called blockbuster drugs, such as sidenafil (Viagra) or atorvastin (Lipitor), are slowing down due to loss of patent protection[81]. Large pharma industries are fundamentally changing in favour of a new business model going from "blockbusters to niche busters" [82]. Powerful pharmaceutical companies like Pfizer, Novartis, Eli Lilly and GlaxoSmithKline are already involved in the rare disease sector where orphan drug legislation exists (but not in Canada) in order to develop and commercialize new therapies[83].

There seems to be recurrent strategies on the part of Ministers of Health in Canada triggering false hopes in patients affected with rare diseases by announcing future policies. In fact, on October 3rd 2012, the Minister of Health, Leona Aglukkaq from the then Conservative government, made the following announcement during a press conference:

> A regulatory framework designed and used specifically to approve drugs to treat small, vulnerable populations will more effectively address this need. A key focus of this new

[80] Shannon Gibson, Hamid R Raziee & Trudo Lemmens, "Why the Shift? Taking a Closer Look at the Growing Interest in Niche Markets and Personalized Medicine: Why the Shift?" (2015) 7:1 World Medical & Health Policy 3.
[81] R Collier, "Bye, bye blockbusters, hello niche busters" (2011) 183:11 Canadian Medical Association Journal at E697.
[82] *Ibid*.
[83] Elie Dolgin, "Big pharma moves from 'blockbusters' to 'niche busters'" (2010) 16:8 Nature Medicine 837.

> approach will be on international information-sharing and collaboration for the development and regulation of orphan drugs[84].

The Orphanet-Canada reference portal was indeed created. It is now part of global Orphanet, and provides information regarding rare diseases for the Canadian population[85]. There are nearly 300 orphan drugs on the market in Europe and the United States, but only 50% of these have received market authorization from Health Canada[86]. Still, four years later, this announcement from the Minister of Health has not led to any concrete regulatory framework or policies for rare diseases.

1.1.3.1 Heading towards More Transparency: *Vanessa's Law*

In hoping for a new approach towards the authorization of orphan drugs in Canada, Bill C-17 was deposited in the House of Commons in 2013. It received Royal Assent in 2014, and is now known as "Vanessa's Law[87]. The law is named after Vanessa Young, the daughter of Terrence Young (a Member of Parliament) who died from an adverse drug event in 2000. The purpose of this Bill was to amend the *Food and Drug*

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[84] *Supra* note 34; "Pharma in brief - Canada: New orphan drug pathway to be released for comment in Canada", online: <http://www.nortonrosefulbright.com/knowledge/publications/71211/pharma-in-brief-canada-new-orphan-drug-pathway-to-be-released-for-comment-in-canada> (Accessed April 2 2016).

[85] "Orphanet-Canada Governance", online: <http://www.orpha.net/national/CA-EN/index/governance/>.(Accessed April 3 2016).

[86] "Regroupement québécois des maladies orphelines (RQMO) ", 2014, Québec, online : <www.rqmo.org/PDF/Document_preparatoire_diner-conference_21_fevrier.pdf> (Accessed April 3 2016). It should be mentionned that there is no orphan drug list available in Canada. It is difficult to know the exact number.

[87] *House Government Bill - Bill C-17 - Royal Assent (41-2)* [*House Government Bill - Bill C-17 - Royal Assent (41-2)*]. *Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)* (S.C. 2014, c. 24). An Act to amend the Food and Drugs Act, This bill was last introduced in the 41st Parliament, 2nd Session, which ended in August 2015, "Bill C-17 (Historical) | openparliament.ca", online: <https://openparliament.ca/bills/41-2/C-17/>. (Accessed April 3 2016).

Act regarding therapeutic products in order to improve safety. In order to do so, various measures were presented such as "to strengthen safety oversight of therapeutic products throughout their life cycle; to improve reporting by certain health care institutions of serious adverse drug reactions and medical device incidents that involve therapeutic products; and to promote greater confidence in the oversight of therapeutic products by increasing transparency"[88].

In fact, the introduction of *Vanessa's Law* was seen as a breath of fresh air, and a new beginning in the transparency process for drug safety in Canada[89]. A historical review shows that since the inception of regulation for pharmaceutical drugs in 1887, and for nearly 40 years until the 1920s, specific bulletins identifying contaminated drugs (by names, "shop-keeps") were published. These bulletins were sent to "news media, physicians, pharmacists and regulatory scientists" to ameliorate drug preparation[90]. In 1920, a restructuration took place with Canada's new Department of Health and the *Food and Drugs Act*[91] was passed. The identification of contaminated pharmaceutical drugs was no longer part of the public domain. Even until the 40's and 50's, this information was kept secret until it reached the legal system[92]. A more recent example of the major consequences on people's health due to the concealment process involved is the "Vioxx® (rofecoxib, from Merck and Co.) scandal", where the anti-pain drug was

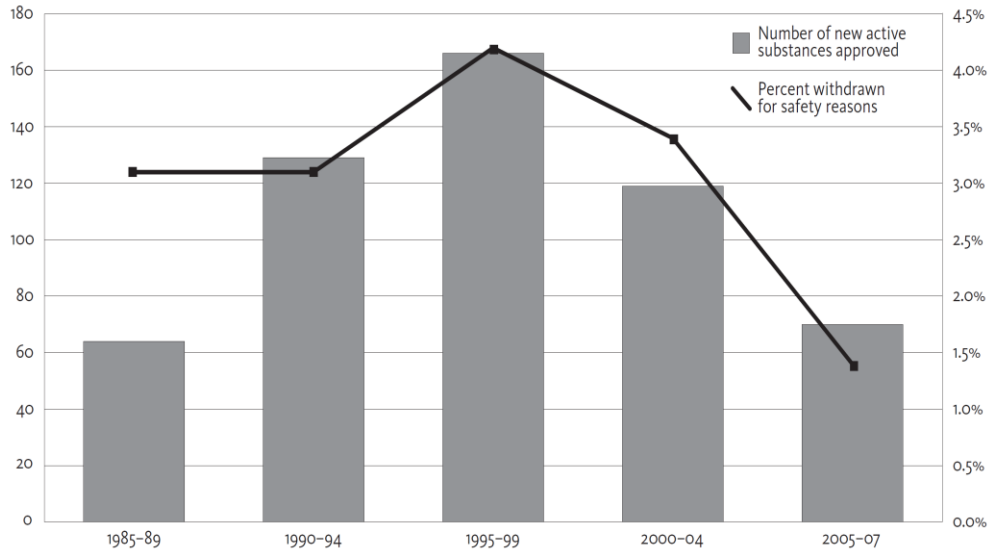
[88] Health Canada Government of Canada, "Amendments to the Food and Drugs Act: Guide to New Authorities (power to require & disclose information, power to order a label change and power to order a recall)", (25 March 2015), online: <http://www.hc-sc.gc.ca/dhp-mps/legislation/unsafedrugs-droguesdangereuses-amendments-modifications-eng.php>. Preamble to *Vanessa's Law*. (Accessed April 5 2016).
[89] M Herder, "Reinstitutionalizing transparency at Health Canada" (2016) 188:3 Canadian Medical Association Journal at 218.
[90] *Ibid*.
[91] *Supra* note 58 s. C.05.010.
[92] Matthew Herder, "Denaturalizing Transparency in Drug Regulation" (2015) 8:2 McGill JL & Health S57; Also, J Lexchin, "Transparency in drug regulation: Mirage or oasis?" (2004) 171:11 Canadian Medical Association Journal 1363.

provided for arthritis-related ailments. It is estimated that more than half a million US citizens[93] and tens of thousands of Canadians[94] died from cardiac arrest due to "a risk that regulatory officials had previous knowledge of but nevertheless kept confidential"[95]. Physicians, as well as patients, were not informed of the serious adverse events directly related to Vioxx, even if Merck knew about potential deadly side effects in 1999 before launching the drug on the market[96].

Figure 3 shows the number of new active drugs approved in Canada, which varied from approximately 60 to 160 drugs from 1985 to 2007, in relation to the percentage of withdrawals due to safety reasons over a 12-year span. Results show that the percentage of withdrawal for safety reasons varied approximately from 1.7 to 4.2%. It is encouraging that withdrawal percentages are reduced from 2000 to 2007[97].

[93] Alexander Cockburn, "When half a million Americans died and nobody noticed", online: *The Week UK* <http://www.theweek.co.uk/us/46535/when-half-million-americans-died-and-nobody-noticed>. (Accessed April 3 2016).
[94] *Supra* note 89.
[95] *Ibid.*
[96] *Supra* note 93.
[97] Joel Lexchin & Canadian Centre for Policy Alternatives, *Drug safety and Health Canada going, going…gone?* (Ottawa: Canadian Centre for Policy Alternatives, Centre canadien de politiques alternatives, 2009) at 6.

Figure 3. Safety Withdrawals as a Percentage of Drug Approvals from 1985–2007

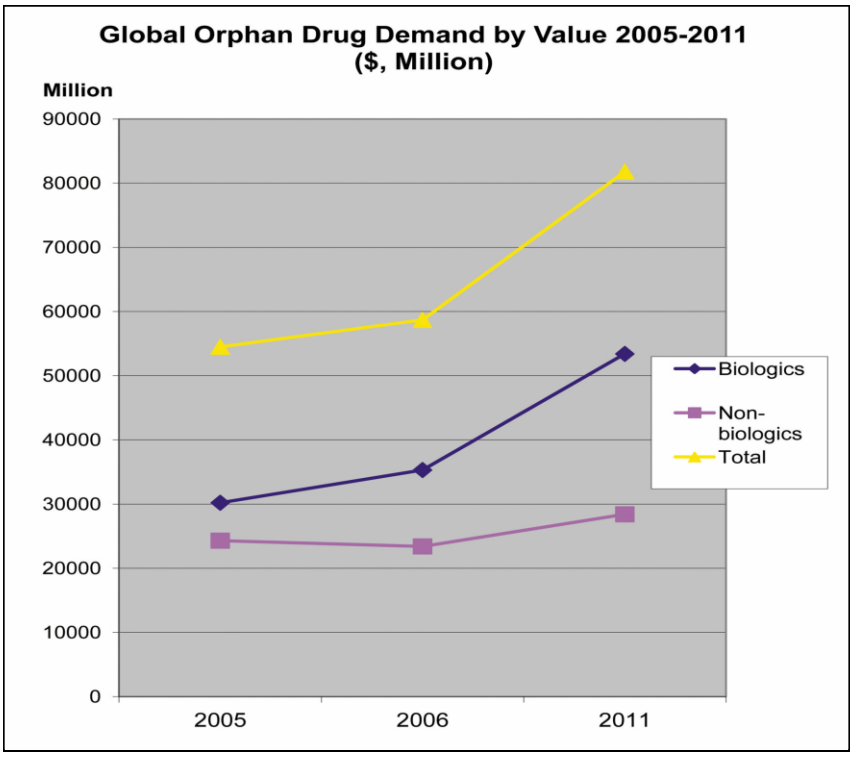


Source: Canadian Centre for Policy Alternatives 2009

Moreover, it is worth noting that Health Canada can provide "a public warning about a drug without the agreement of the company involved, but it cannot directly compel the company to revise the label of its product to reflect new safety information". Considering the global growth of the orphan drug market (Figure 4)[98], this is an issue which should not be taken lightly because of the increased demand of orphan drugs and the added necessity for safety measures and warnings to physicians and patients involved. Briefly, Figure 4 shows an increase in drug demands for biologics, which are complex manufactured products from animals or through the use of animals or microorganisms, and non-biologic drugs which are chemically synthesized. Therefore, it is quite understandable that orphan drugs, as well as any drug put on the market, should be optimally evaluated by Health Canada (and the FDA in the US) before they reach the market.

[98] Sinéad M. Murphy et al, "Unintended effects of orphan product designation for rare neurological diseases" (2012) 72:4 Annals of Neurology 481, at 12. doi:10.1002/ana.23672

Figure 4. Global Growth of the Orphan Drug Market



Source: BBC Research

Under *Vanessa's Law*, the Health Minister in Canada is now authorized to provide confidential business information if it involves the safety and protection of its Canadian constituents:

> (3) The Minister may disclose confidential business information about a therapeutic product without notifying the person to whose business or affairs the information relates or obtaining their consent, if the purpose of the disclosure is related to the protection or promotion of human health or the safety of the public and the disclosure is to:
> (a) a government;
> (b) a person from whom the Minister seeks advice; or
> (c) a person who carries out functions relating to the protection or promotion of human health or the safety of the public [99].

[99] *Supra* note 87 s. 21.1(3).

This measure could allow physicians to enquire about adverse events before providing a particular drug to a patient or enrolling patients in a research project. Furthermore, it could provide information to patients in order for them to give an informed consent to research projects involving orphan drugs. Researchers could also be better appraised of the potential risks and benefits of a particular drug while performing their research studies.

Even if the safety and protection of Canadian citizens have been promoted with *Vanessa's Law*, it would have been a good opportunity to introduce a policy framework for orphan drugs, but unfortunately, this was not the case[100]. Even if over the years the federal government has been inclined to modify the *Food and Drug Act*, it seems that the orphan drug framework is a persistent issue, which it does not want to tackle[101].

1.1.3.2 Canadian Agency for Drugs and Technologies in Health

According to the Canadian Agency for Drugs and Technologies in Health (CADTH)[102], a document written by Health Canada, in 2012, proposed a definition for an "orphan drug" which would rely on the prevalence and the severity of the disease[103]. For example, a child weighing 20 kilograms (Kg) receiving Aldurazyme® (Laronidase),

[100] Jill Daley, "Pharma in brief - Status update: Regulatory and policy changes to create orphan drug environmentfor Canada", September 2014, online: <http://www.nortonrosefulbright.com/knowledge/publications/120679/pharma-in-brief-status-update-regulatory-and-policy-changes-to-create-orphan-drug-environment-for-canada>. (Accessed April 2 2016)
[101] *Ibid*.
[102] Canadian Agency for Drugs and Technologies in Health, "About CADTH | CADTH.ca", online: <https://www.cadth.ca/about-cadth>. (Accessed April 3 2016).
[103] Canadian Agency for Drugs and Technologies in Health, Drugs for rare diseases: evolving trends in regulatory and health technology assessment perspectives. Ottawa; CADTH; 2013 Oct [updated 2016 Feb]. (Environmental scan; issue 42) at 6 Online: <https://www.cadth.ca/sites/default/files/pdf/ES0300_Rare_Disease_Drugs_e.pdf_> (Accessed April 3 2016).

an orphan drug prescribed in patients affected with a lysosomal storage disorder called Hurler disease (Mucopolysaccharidosis type I), and given at 0.5 mg/Kg weight/week by infusion will cost $400,000 CAD per year, and for an adult weighing 70 kilos, the cost will be $1,200,000 CAD[104] per year. Considering the high cost involved for patients receiving orphan drugs, it is understandable that the prevalence of an orphan disease plays an important role in the process and criteria to obtain access to this orphan drug.

The CADTH is an independent, non-profit organization with a mission "to provide timely, relevant, rigorously derived, evidence-based information to decision makers and support for the decision-making processes with areas of focus which include assessing the cost and health effectiveness of drugs and health technologies and identifying and promoting best practices in drug prescribing and use"[105]. CADTH was created in 1989 (formerly under the name Canadian Coordinating Office for Health Technology Assessment "CCOHTA")) and is financially supported by federal, provincial and territorial governments. The independence in CADTH's decision-making was confirmed in 1998 in an Ontario court-case *versus* the pharmaceutical company Bristol-Myers-Squibb Canada[106].

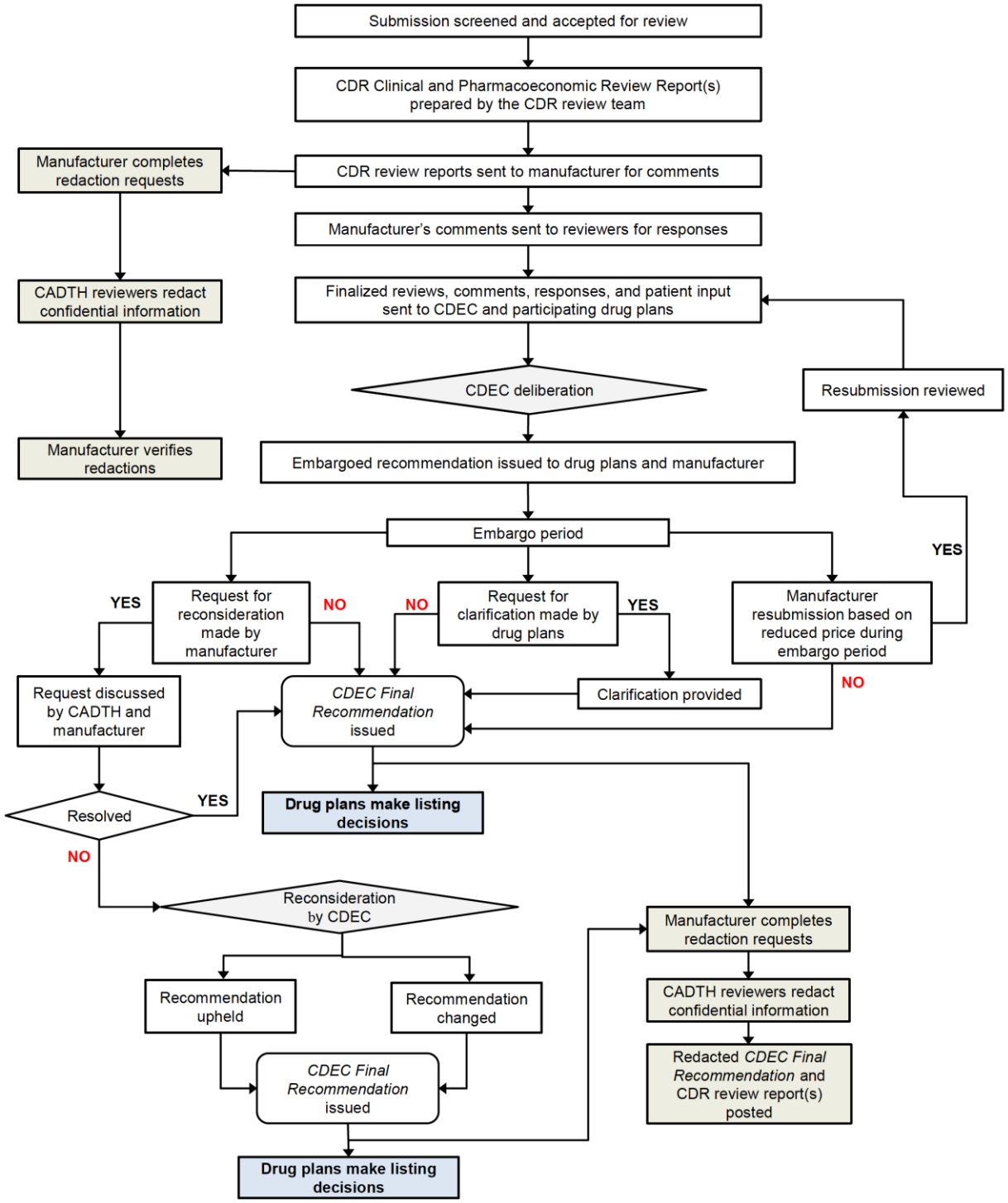
It is worth noting that CADTH plays an important role in rare diseases and orphan drugs, since it offers prospective models to provide guidance in the decision-making process for financing these drugs by establishing the natural history of the disease (if available), the optimal time to give a drug to affected patients, and the group

[104] *Ibid* at 21. See also on the same subject: "CIHR New Emerging Team | The Changing Landscape of Treatments for Rare Diseases", online: <http://rare-diseases.ca/>. (Accessed April 3 2016).
[105] "INAHTA | CADTH – Canadian Agency for Drugs and Technologies in Health -Mission", online: <www.inahta.org> (Accessed April 3 2016). See also, *Supra* note 102.
[106] *Bristol-Myers Squibb Canada Inc v Canadian Coordinating Office for Health Technologies Assessment*, 1998 CanLII 14796 (ON SC) online: <http://canlii.ca/t/1w8r0>.

of patients who would benefit from the treatment[107]. Moreover, since September 2003, CADTH is also responsible for the Common Drug Review (CDR). The CDR is a "national process that provides participating federal, provincial and territorial drug plans with a systematic review of the best available clinical evidence, a critique of manufacturer-submitted pharmacoeconomic studies and a formulary listing recommendation made by the Canadian Drug Expert Committee (CDEC) or Canadian Expert Drug Advisory Committee (CEDAC)"[108]. It also "provides more consistent and rigorous reviews of new prescription drugs, so that public drug benefit coverage will be directed to the most cost-effective and therapeutically beneficial drugs. All jurisdictions are participating except Québec"[109]. The CDEC's recommendations are non-binding to drug plans, therefore each province decides on its own drug-listing decisions of the CDEC, but also taking into consideration jurisdictional priorities and financial resources[110]. Considering the various possibilities of drug review that include orphan drug as well, Figure 5 provides an accurate flowchart of the overall CDR mechanism involved[111]. It is a multi-level complex process starting from the submission of the application to the final decision upon the CDEC's final recommendations.

[107] *Supra* note 102.
[108] "Pharmaceutical HTA and Reimbursement Processes - Canada", online: <https://www.ispor.org/HTARoadMaps/CanadaPharm.asp>. (Accessed April 3 2016).
[109] Health Canada Government of Canada, "ARCHIVED - Common Drug Review - Health Care System", (28 May 2004), online: <http://www.hc-sc.gc.ca/hcs-sss/pharma/mgmt-gest/cdr-emuc-eng.php>. (Accessed April 2 2016).
[110] "CADTH Commong Drug Review | Procedure for the CADTH Common Drug Review", August 2014, at 2, online: <https://www.cadth.ca/media/cdr/process/CDR_Procedure.pdf>. (Accessed June 2 2016).
[111] *Ibid* at 4.

Figure 5. CADTH Common Drug Review Process



CDEC = Canadian Drug Expert Committee; CDR = CADTH Common Drug Review.

Source: CADTH Common Drug Review, 2014

There is also the pan-Canadian Oncology Drug Review (pCODR) that reviews only cancer drugs. It reviews the clinical evidence, cost-effectiveness in order to make recommendations to provinces, (except Québec)[112].

In 2010, the creation of the pan-Canadian Pharmaceutical Alliance (pCPA), was part of an endeavor from the Council of the Federation's Health Care Innovation Working Group (HCIWG) aimed at creating "greater value for publicly funded drug programs and patients". Consequently, all brand name drugs considered for funding by the CDR are considered for negotiation through the pCPA. Numerous advantages are targeted by joining forces with all provinces and territories allowing a "combined negotiating power of drug plans"[113]. The main advantages are the increased access to drug treatment options, the possibility to achieve reduced drug costs and consistent pricing, and obtain more consistent criteria for drug coverage all over Canada. All provinces and territories work together for generic and brand name drugs and, as of March 2015, $490 million in annual combined savings was estimated for these drugs[114]. Considerable efforts by CADTH, CDR and pCPA are dedicated to reach better values for public drugs, including drugs for rare diseases.

1.1.3.3 Patented Medicine Prices Review Board

In contrast to the CADTH, which has no binding authority but which plays an important role regarding public reimbursement, the Patented Medicine Prices Review

[112] "CADTH pan-Canadian Oncology Drug Review | CADTH.ca", online: <https://www.cadth.ca/about-cadth/what-we-do/products-services/pcodr>. (Accessed April 3 2016).
[113] "Canada's Premiers - The pan-Canadian Pharmaceutical Alliance", online: <http://www.pmprovincesterritoires.ca/en/initiatives/358-pan-canadian-pharmaceutical-alliance>. (Accessed April 6 2016)
[114] *Ibid*.

Board (Board) is an independent quasi-judicial body under the *Patent Act*[115]. The Board "protects the interests of Canadian consumers by ensuring that the prices of patented medicines sold in Canada are not excessive"[116]. In *Sanofi Pasteur Limited v. Canada (Attorney General)* at paragraph 6, it was stated at the Federal Court that: "It is clear that Parliament's intention in creating the Board was for it to control the market power of the monopoly created by the exclusivity of a patent"[117], reinforcing the duties of the Board towards patents pertaining to a "medicine". This being said, the Board's mandate is not to set prices for patented medicines sold in Canada, but to make sure that the price a patentee is selling the drug for is not, in the Board's opinion, excessive; therefore the Board is acting as a "watchdog"[118]. However, it has no power to regulate excessive prices of non-patented drugs and that includes all non-patented drugs sold in Canada[119]. To determine if a price is excessive or not, the Board collects information provided by the patentee in accordance with the regulations[120] and conducts price tests. The Board performs a strict and thorough evaluation of a specific medicine and also compares the cost of the latter medicine sold in Canada with prices from other countries. In order to further explain how the Board proceeds in determining whether a price is excessive, it is better to have a concrete example of a drug product intended to treat a rare disease. Soliris® (eculizumab) is a drug manufactured by Alexion Pharmaceutical Inc. for the treatment of two rare diseases.

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[115] *Patent Act*, R.S.C. 1985, c. P-4

[116] Patented Medicine Prices Review Board – "Mandate and Jurisdiction", (26 June 2014), online: <http://pmprb-cepmb.gc.ca/about-us/mandate-and-jurisdiction>. (Accessed April 4 2016)

[117] *Sanofi Pasteur Limited v Canada (Attorney General)*, 2011 FC 859 online: <http://canlii.ca/t/fm9hw>. It should be noted that marketing authorization in Canada and patents do not go hand in hand.

[118] *Patent Act*, *supra* note 115 SS. 80-87; *Pfizer Canada Inc v Canada (Attorney General)*, 2009 FC 719 at para 11 online: <http://canlii.ca/t/24rrg>. The expression "watchdog" was used by Minister of Consumer and Corporate Affairs Harvie Andre (See para 60 in *Pfizer*)

[119] Patented Medicine Price Review Board, "Frequently Asked Questions", (26 June 2014), online: <http://pmprb-cepmb.gc.ca/about-us/frequently-asked-questions> (Accessed April 8 2016); *Celgene Corp. v. Canada (Attorney General),* 2011 SCC 1, [2011] 1 S.C.R. 3

[120] *Patent Act*, *supra* note 115, SS. 80-82

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a serious and life-threatening condition leading to the destruction of red blood cells, and Atypical Hemolytic Uremic Syndrome (aHUS) is a serious and debilitating condition causing blood clots in small vessels[121]. Alexion received a NOC from Health Canada in January 2009 for PNH, whereas the NOC for aHUS was issued in 2013. Soliris was sold in Canada from 12 June 2009 at a marketing price of $224.73 CAD/mL. It was then, and it is still considered one of the most expensive drugs in the world[122]. A Canadian Patent (No. 2189015) was granted to Alexion in April 2010, which expired in May 2015[123]. Alexion can exercise rights according to subsection 79(1) of the Patent Act[124]. Therefore Alexion is entitled to:

> […] the benefit of the patent for that invention and includes, where any other person is entitled to exercise any rights in relation to that patent other than under a license continued by subsection 11(1) of the Patent Act Amendment Act, 1992, that other person in respect of those rights; […][125].

In regards to the patentee, the Board evaluates the pricing information in reference to the 2010 Compendium of Guidelines, Policies and Procedures ("2010 Guidelines"), and the Highest International Price Comparison ("HIPC") test[126]. The Board also compared the

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[121] Matthew A Lambert & William J J Finlay, "Chapter 14. Soliris (Eculizumab): Discovery and Development" in David C Pryde & Michael Palmer, eds, *RSC Drug Discovery* (Cambridge: Royal Society of Chemistry, 2014) 401, see *supra* note 53; "Soliris® (eculizumab) | Alexion, Rare Disease Leader", online: <http://alexion.com/Products/Soliris>. (Accessed April 3 2016)

[122] "The real cost of the world's most expensive drug", online: <http://www.cbc.ca/news/thenational/the-real-cost-of-the-world-s-most-expensive-drug-1.3126338>. (Accessed April 3 2016)

[123] According to *Patent Act*, *supra* note 115, s. 83(7):"No order may be made under this section in respect of a former patentee who, more than three years before the day on which the proceedings in the matter commenced, ceased to be entitled to the benefit of the patent or to exercise any rights in relation to the patent". That said, the Board can make an order since it falls within the three year period after the expired patent:

[124] *Patent Act*, *supra* note 115 s. 79(1)

[125] *Ibid.*

[126] Patented Medicine Prices Review Board, "Compendium of Policies, Guidelines and Procedures - Updated June 2015", (30 April 2014), online: <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=492>. (Accessed April 3 2016)

price of Soliris sold in other countries, to the National Average Transaction Price (N-ATP). In its statement of Allegations, the Board alleged that Alexion was selling Soliris "at a price higher than in the United States, where Soliris was sold below the international median price among the comparator countries"[127]. Moreover, Alexion was given the opportunity to adjust the price of Soliris, which they declined. In a reply argument, Alexion stated that the allegations of the Board were outside the raised pleadings, and therefore, Alexion filed a notice of application at the Federal Court of Canada. In addition, Alexion went a step further and challenged the Board's power alleging that it was invalid, under sections 83 through 87(1) of the *Patent Act*[128], because it exceeded the authority granted to the federal government pursuant to the *Constitution Act, 1867*[129]. This case is still pending before the Court. Nevertheless, it raises the question of how powerful and unwilling pharmaceutical companies, such as Alexion, a US company, are to decrease the price of their drugs. Moreover, it comes to mind that the Board has limited power over patented medicine. Big pharmaceutical companies have the means and strategies to argue for an extended length of time in Court in order to maintain excessive prices for drugs. In fact, Alexion's reported net product sales was $665 US million for Soliris in the first quarter of 2016[130].

In recent years, exorbitant prices have reached new highs when patents for pharmaceutical drugs expire. Prices for old, off patent drugs are at levels that no one has

[127] Patented Medicine Prices Review Board, "Statement of Allegations of Board Staff | in the matter of the Patent act, R.S.C., 1985, c. P-4, as amended and | in the matter of Alexion Pharmaceuticals Inc ("the Respondent") and the medicine "Soliris" " January 15 2015.
[128] *Patent Act*, *supra* note 115.
[129] *Constitution Act*, 1867, 30 & 31 Vict., c.3 (R.-U.)
[130] "Alexion Reports First Quarter 2016 Results | Alexion Pharmaceuticals, Inc", online: <http://news.alexionpharma.com/press-release/financial-news/alexion-reports-first-quarter-2016-results>.(Accessed April 3 2016)

ever expected before. An example of this is Turing Pharmaceuticals, "the company has the power to set a high price for Daraprim because the drug's limited patient population, the absence of competing manufacturers, and a lack of therapeutic alternatives have all created an effective monopoly"[131]. In fact, the price of Daraprim, a medication to treat life-threatening infections went from $13.50 to $750 US per pill, an increase of 5500% for a drug off patent since the 1970s[132]. In Canada, the Board has no authority once drugs are off patent and expired for longer than 3 years, therefore, pharmaceutical companies are paving the way to increase prices at exorbitant levels[133].

1.1.3.4 Special Access Programme (SAP)

Health Canada has for a long time neglected the possibility of creating specific orphan drug legislation. In a policy statement in 1996, Health Canada evaluated the issue regarding rare diseases and decided to reject the possibility of any orphan drug legislation on the grounds that the system already in place was sufficient. The Health Canada *status quo* in decision-making stems in part from the fact that over 63% of US designated orphan drugs were available in Canada[134]. Moreover, the analysis of Health Canada's decision led to the following statement:

> […] (ii) the high costs of orphan drugs could be an obstacle to patient access; and (iii) the Canadian

[131] Naren P Tallapragada, "Off-patent drugs at brand-name prices: a puzzle for policymakers" (2016) 3:1 Journal of Law and the Biosciences at 239.
[132] The Globe and Mail, "Experts raise alarm over high drug prices, could force new rules", online: <http://www.theglobeandmail.com/news/national/experts-raise-alarm-over-high-drug-prices-could-force-new-rules/article26556253/>. (Accessed June 2 2016)
[133] *Patent Act*, *supra* note 115 s. 83(7)
[134] Orphan Drug Policy. Ottawa (ON): Drugs Directorate, Health Canada; January 16 1997. [letter sent to associations] File no: 96-037419; Durhane Wong-Rieger, "Canada's long journey toward an Orphan Drug Framework", (2013) no. 20(2) *Advocate*, at 20. The *Orphan Drug Framework* has still not been implemented in Canada.

> population was not large enough to support significant research and development in the area"[135].

This clearly shows that Canadian federal authorities were depending on the US for R&D for orphan drugs and accepted these latter drugs in Canada when they were approved in the US. The statement referring to the fact that the Canadian population was not large enough to support R&D is a total misconception and bad use of taxes provided by Canadians for their health system. Put bluntly, relying on resources of another country before investing in R&D for orphan drugs might not be in the best interest of the Canadian healthcare system. Furthermore, it was mentioned in the 1996 statement: "There has not been significant pressure from industry or special interest groups in Canada to develop an Orphan Drug policy"[136].

Canadians had access to orphan drugs that were either marketed through the regular process or approved through the SAP, previously called Emergency Drug Release Programme, which has been in effect since 1966. In our opinion, the rationale for lacking an orphan drug policy was, and still is, probably due to the existence of the SAP.

Health Canada's Special Access Programme:

> […] considers requests for access to drugs that are unavailable for sale in Canada from practitioners treating patients with serious or life-threatening conditions when conventional treatments have failed, are unsuitable or unavailable.[137]

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[135] Richard Y. CHEUNG, Jillian C. COHEN et Patricia ILLINGWORTH, " Orphan drug policies: implications for the United States, Canada, and developing countries ", (2004) 12 *Health Law J* 183 at 190.
[136] *Supra* note 134 at 9.
[137] Health Canada, "Special Access Programme – Drugs". Online: <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapfs_pasfd-eng.php>. (Accessed April 2 2016) Guidance Document for Industry and Practitioners - Special Access Programme for Drugs Ottawa, Health Canada, 2013, online: <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapg3_pasg3-eng.php> (Accessed April 2 2016). See also *supra* note 59 at 114.

Orphan drugs that have yet to be authorized in Canada fall under the SAP, under articles C.08.010 and C.08.011 of the *Food and Drug Regulations,* which is part of the Sale of New Drug for Emergency Treatment[138]:

> **C.08.010** (1) The Director may issue a letter of authorization authorizing the sale of a quantity of a new drug for human or veterinary use to a practitioner named in the letter of authorization for use in the emergency treatment of a patient under the care of that practitioner, if:
>
> a) the practitioner has supplied to the Director information concerning:
>
> i) the medical emergency for which the drug is required;
> ii) the data in the possession of the practitioner with respect to the use, safety and efficacy of that drug;
> (iii) the names of all institutions in which the drug is to be used, and
> (iv) such other data as the Director may require; and
>
> (b) the practitioner has agreed to:
>
> (i) report to the manufacturer of the new drug and to the Director on the results of the use of the drug in the medical emergency, including information respecting any adverse reactions encountered, and
> (ii) account to the Director on request for all quantities of the drug received by him.
>
> (1.1) The Director shall not issue a letter of authorization under subsection (1) for a new drug that is or that contains a restricted drug as defined in section J.01.001.
>
> (2) The Director shall, in any letter of authorization is-sued pursuant to subsection (1), state
> (a) the name of the practitioner to whom the new drug may be sold;
> (b) the medical emergency in respect of which the

[138] *Supra* note 58, s. C.08.010 and s. C.08.011.

> new drug may be sold; and
> (c) the quantity of the new drug that may be sold to that practitioner for that emergency.
>
> **C.08.011** (1) Notwithstanding section C.08.002, a manufacturer may sell to a practitioner named in a letter of authorization issued pursuant to section C.08.010, a quantity of the new drug named in that letter that does not exceed the quantity specified in the letter.
>
> (2) A sale of a new drug made in accordance with subsection (1) is exempt from the provisions of the Act and these Regulations.

In order to access a drug via SAP, a practitioner, usually a licensed physician must complete and submit a multipart Special Access Request (SAR) form. The SAR form contains the practitioner and shipping information, the drug and manufacturer information, the patient information, as well as the clinical rationale for requesting the drug, including references for its safety and efficacy and three attestations for the requesting practitioner[139]. The SAP overstates that it processes most requests within 24 hours of receipt, although a triage system is used and processing time may take longer depending on the volume of SARs received. It is pertinent to mention that the request is only for an exact amount of the drug for the treatment of a single patient and cannot extend beyond a maximum of six months. If the treatment is for a longer period of time, it will require a second request form. Once the screening and reviewing process is completed, the SAP will issue one of the following decisions: authorization, incomplete, cancellation, withdrawal or denial. In a recent court case, it was decided that the Court cannot intervene in terms of discretionary regulation according to article C.08.010

[139] Health Canada Government of Canada, "Health Canada's Special Access Programme: Special Access Request - Form A", (2 August 2002), online: <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapf1_pasf1-eng.php>. (Accessed April 2 2016)

regarding the non-obligation to deliver SAP authorizations in the SAP programme[140]. The reason for not intervening is that it would be illegal and in violation of the provisions according to the aforementioned regulations "which stipulate certain conditions that must be met by a physician requesting access before the Director General can exercise his discretion"[141].

Notwithstanding the decision, if the practitioner's request is authorized, he can therefore ask for the drug from the manufacturer. However, the manufacturer is not compelled in any way to accept the request and has the right to place restrictions or conditions on the release of the drug.

A major issue revolves around the fact that the SAP has clearly created an administrative burden on the practitioner that is time-consuming and labour-intensive, it is thus a marked disadvantage, in this case, for patients with rare diseases[142]. Moreover, the treatment for rare diseases is often given throughout the lifetime of the patient and, if authorized by the SAP, the practitioner has to fill out requests that only last for six months[143]. In a normal scenario, one can imagine a practitioner working in a large medical centre having forty patients or more with several rare diseases and continuously having to complete forms, twice a year for each patient, over time. This is a tremendous administrative burden for the physician and the healthcare system, considering the paperwork and different administrative officers involved. Ironically, the Minister of Health in Canada, in 2012, recognized that the SAP was problematic regarding orphan drugs:

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[140] *Delisle v Canada (Attorney General)*, 2004 FC 788 online: <http://canlii.ca/t/1jhdk>.
[141] *Ibid* at paragraph 14.
[142] Personal communication from physicians treating many patients with rare diseases.
[143] *Supra* note 137.

> Today, when an orphan drug is not available in Canada, the patient's doctor can apply individually for each patient through Health Canada's Special Access Programme. While facilitating access - the current approach also represents a significant burden to the healthcare system[144].

A thorough analysis of articles C.08.010 and C.08.011 of the *Food and Drug Regulations* mentioned above shows that they were designed for new drugs, as well as for the emergency treatment of a patient. SAP enables access to new drugs not yet on the Canadian market where physicians can monitor closely patients for adverse drug events[145]. In fact, physicians need to provide a medical follow-up on the outcome of treatment with respect to the requested drug.

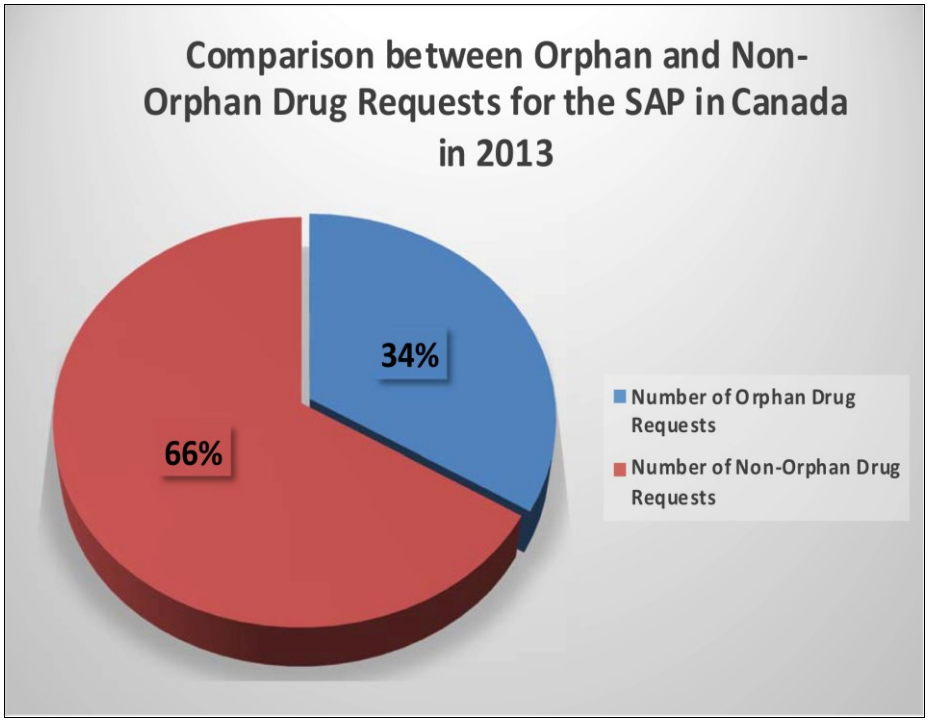
According to the *Access to Information Act*[146]*,* an application was submitted to Health Canada to obtain a list of every drug where a SAP request was granted for the year 2013 (Appendix 1). This list contains the product name, as well as the number of requests authorized for each of the drugs listed, which are shown according to the prescription dose. Therefore, one specific drug might have three different doses, thus leading to three different entries (requests) in the list provided by Health Canada. From January 1st until December 2013, a total of 431 drugs were submitted and authorized *via* the SAP. Unfortunately, this list did not distinguish orphan drugs from non-orphan drugs, therefore there are no specific indications for orphan drugs in Canada.

Hence, the key question is: how many of these drugs, listed by Health Canada, had or have designations for orphan drugs in Europe and the USA? In order to answer this question we devised a table compiling data from drugs, which have been granted an

[144] *Supra* note 34.
[145] *Teva Canada Limited v. Canada* (Health), 2012 FCA 106 (CanLII)
[146] *Access to Information Act*, R.S.C., 1985, c. A-1.

orphan drug designation either by the Orphanet database[147] or by the FDA database[148] (Appendix 2). This table is comprised of different categories, namely the drug or product name and the alternative drug name; the orphan drug number from Orphanet if available; the country of orphan designation; the dose; and the number of SAP requests authorized during a specific year. Our results for 2013 show that the total number of requests for orphan and non-orphan drugs authorized by SAP is 14,532. Orphan drug accounted for 4,912 (33.8%), and 9,620 (66.2%) for non-orphan drug SAP authorizations (Figure 6).

Figure 6. Comparison of the Percentages between the Orphan and Non-Orphan Drug Authorized Requests through the Special Access Programme by Practitioners in Canada for 2013



Source: Our analysis

[147] "Orphanet: Orphan drugs", online: <http://www.orpha.net/consor/cgi-bin/Drugs.php?lng=EN>. (Accessed April 4 2016).
[148] U.S. Food and Drug Administration, "Search Orphan Drug Designations and Approvals", online: <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/>. (Accessed March 17 2016).

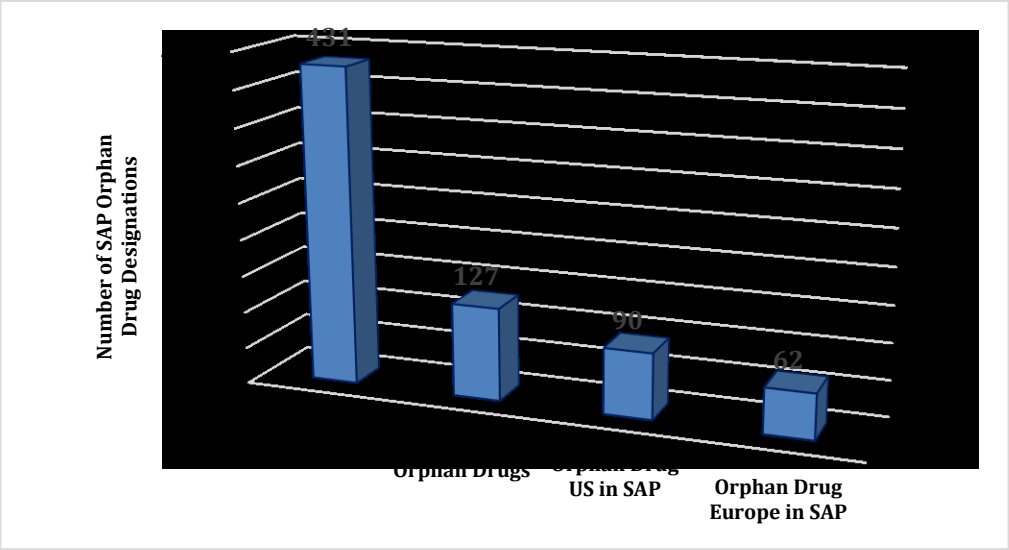
The table in Appendix 2 also shows that for one specific drug, there might be two countries or more of origin designations. Nevertheless, only the selection of Europe and US designations were taken into account in this table. For example, Naglazyme® (galsulfase from BioMarin Pharmaceuticals Inc.), is provided for mucopolysaccharidosis type VI, (also called Maroteaux-Lamy syndrome) patients. This rare genetic lysosomal storage disorder, has a designation in the US while the designation in Europe was eventually withdrawn. Another example is the drug Orfadin (nitisinone) provided by the Swedish Orphan Biovitrum company for alkaptonuria or tyrosinemia type I patients. This drug has a designation in the US and Europe for alkaptonuria, but in Europe it had the designation withdrawn for tyrosinemia type I. Orfadin is usually prescribed in Québec (and elsewhere) for tyrosinemia type I patients, considering the founder effect (i.e. when a group of individuals comes from a few members of an original population carrying a gene with a unusually high frequency) known in the province, and consequently the very high incidence of 1/16,667 live births, and 1/1,846 in the specific region of the Saguenay-Lac-Saint-Jean region for this disease (worldwide average incidence for tyrosinemia type I is 1/100,000)[149].

There were a total of 431 drugs in the SAP list. Out of these, 127 were orphan drug designated (Figure 7). A total of 90 of these have or had (because of an expiration date exclusivity) an orphan designation drug in the US. In Europe, 62 have an orphan drug designation. The major discrepancy between the total number of SAP orphan drugs (n=127) in Canada and the ones already approved in the US (n=90) and Europe (n=62) reveals a major administrative burden in Canada for patients to have access to the same

[149] Mariève Simoncelli et al, "Cost-Consequence Analysis of Nitisinone for Treatment of Tyrosinemia Type I" (2015) 68:3 Can J Hosp Pharm 210.

drugs, which have already been authorized and distributed throughout other countries. This is mainly due to the fact that US and Europe both have specific legislation encompassing these drugs. Unfortunately, Canada relies on the complex, time-consuming and case-by-case basis "SAP" to allow access to these same orphan drugs for rare disease patients.

Figure 7. Number of SAP Orphan Drug Designations in US and Europe Compared to Total SAP Drugs for 2013



Source: Our analysis

However, a question then arises: are all drugs available through SAP new or experimental drugs? In response to this question, the SAP has established in a policy statement the following:

> Special access by Canadian health practitioners to unauthorized drugs is intended for serious or life-threatening conditions where conventional therapies have

> failed, are unsuitable, or are unavailable either as marketed products or through enrollment in clinical trials[150].

However, the example of Prussian Blue (distributed by Heyl Chemisch-Pharmazeutische Fabrik Gmbh), which is authorized via the SAP process, is not a new drug. In fact, Prussian Blue has been used clinically since the 1960's and approved by the FDA as an orphan drug since 2003. Since the 1960's, the clinical use of Prussian Blue relates to its orphan drug usage. It plays a major role in trapping radioactive/non-radioactive thallium, and radioactive cesium in the intestine to avoid internal radioactive contamination[151]. Prussian Blue shows that some of these drugs are definitely not novel drugs. Therefore, SAP is a poor fit considering that it does not distinguish between "old" and "new" orphan drugs. In fact, Prussian Blue was requested and authorized twice in 2013 through the SAP (See Appendix 1).

It is clear that the importance of drug regulations is to ensure safety and efficacy for patients. However, might the SAP just be a bypass for pharmaceutical companies when drugs are not marketed in Canada? Assuming a drug previously sold in Canada, yet withdrawn from the market not for safety and efficacy issues, but simply because it was unprofitable to the marketer: could the SAP be a bypass to reintroduce the drug at more favorable conditions for the marketer[152]? Among others, pharmaceutical orphan

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[150] *Supra* note 137.

[151] U.S. Food and Drug Administration. "Guidance for Industry, Prussian Blue Drug Products—Submitting a New Drug Application, FDA, January 2003 Clinical Medical", at 1, Online: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072020.pdf> (Accessed April 4 2016).

[152] The example of cycloserine and pyrimethamine, available through SAP, both of which were previously sold in Canada, until they were withdrawn from the market. The reason of withdrawal was not for reasons of safety or efficacy but by the decision of the marketer. We supposed that the SAP could be a favorable option for pharmaceutical companies since the SAP prevents the process of a New Drug Application for a pharmaceutical company and therefore avoids the fees related to the application.

drugs that have never been patented, or marketed in Canada therefore fall into an abyss, where Canadian authorities cannot control excessive costs for these orphan drugs since it is not under the authority of the Patented Medicine Prices Review Board (Board) mentioned previously[153]. The example of Thiola®, an off-patent orphan drug medication for cystinuria, a rare genetic disease causing kidney stones, was successfully requested 75 times in 2013 through the SAP. There has been a significant price increase from US $1.50 per tablet to $30 per tablet, leading patients to pay an estimated cost of $100,000 per year[154]. At the time, the price of Thiola® was not controlled by the Board since it was not patented in Canada, being an off-patent drug. Unfortunately, the Board had no power to control the excessive price which remains at the same price in 2016 leading to difficulty for patients to have a reimbursement of the drug[155].

Although orphan drugs can be authorized through SAP, the reimbursement of these drugs is still another major issue for patients considering their high prices. The burden then becomes a provincial responsibility. "All developed countries with universal healthcare systems provide universal coverage for prescription drugs – except Canada"[156]. It is time to rethink pharmacare policies in Canada, since the situation involves limited allocation by provinces for public subsidies for prescription drugs, and

[153] *Supra* note 119 at 4: "When C obtained the Canadian patent in relation to Thalomid in 2006, the Patented Medicine Prices Review Board ("Board") advised C that it now had jurisdiction to request pricing information from C from the time it first sold Thalomid through the SAP in 1995."
[154] "Imprimis Pharmaceuticals Begins Dispensing Lower Cost Alternative to Thiola®", (2 May 2016), online: *Investor Relations - Imprimis Pharmaceuticals, Inc* <http://imprimispharma.investorroom.com/2016-05-02-Imprimis-Pharmaceuticals-Begins-Dispensing-Lower-Cost-Alternative-to-Thiola>.(Accessed June 3 2016)
[155] ICI Radio-Canada.ca Radio-Canada, "Prix des médicaments : des patients pris en otage", online: <http://ici.radio-canada.ca/audio-video/media-7415567/prix-des-medicaments-des-patients-pris-en-otage>. (Accessed June 5 2016)
[156] Steven G Morgan, Jamie R Daw & Michael R Law, *Rethinking Pharmacare in Canada* ([Toronto, ON]: C.D. Howe Institute, 2013) at 1.

therefore the remaining costs have to be financed either, out-of-pocket or through private insurances.

Some limitations were encountered in this SAP analysis. First, data provided by Health Canada were supposed to be for drugs considered as pharmaceutical, biologic, and radio-pharmaceutical products. Nonetheless, alternative medications were also encountered in the list provided, such as medical maggots or medicinal leeches. These latter medications were requested 21 times and 120 times, respectively, under SAP and were included in the total drugs evaluated in Figures 6 and 7 as non-orphan drugs. Also, some products, such as 714X (trimethylaminohydroxybicycloheptane chloride) requested successfully 21 times through the SAP, is an unconventional therapy for cancer, and was included in the data provided by Health Canada, even if no clinical trials were done and it is banned in the US[157]. As stated previously and in accordance to Health Canada's SAP list, we counted as three medications, a product having three different doses. For example, the drug afatinib (BIBW 2992) had 30, 40, 50 mg was compiled thrice.

In 2012, after the announcement of a regulatory framework for orphan drugs in Canada, an initial draft discussion document was released[158]. The objective of this draft discussion was to "provide context and policy intent for the proposed drug regulatory framework including the details of the proposal"[159]. Even until now, no concrete regulatory framework has yet to be implemented in Canada.

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[157] Elizabeth Kaegi, "Unconventional therapies for cancer 6. 714-X", (1998) 158 CMAJ 1621.
[158] Office of Legislative and Regulatory Modernization. (2012). Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework. Retrieved from <http://www.orpha.net/national/data/CA-EN/www/uploads/Initial-Draft-DiscussionDocument-for-A-Canadian-Orphan-Drug--Regulatory-Framework.doc>.
[159] *Ibid*.

1.2 At the Provincial Level

In Canada, "the administration and delivery of health care services is the responsibility of each province and territory, guided by the provisions of the Canada Health Act"[160]. Federal fiscal transfers are provided to provinces to enable them to fulfill their responsibilities[161]. In order to qualify for a full cash contribution, provinces must meet five fundamental criteria: public administration; comprehensiveness, universality, portability and accessibility[162]. Accessibility is defined as: "The degree to which individuals are inhibited or facilitated in their ability to gain entry to and to receive care and services from the health care system. Factors influencing this ability include geographic, architectural, transportational, and financial considerations, among others"[163]. Moreover, according to the comprehensiveness criterion of the *Canada Health Act*:

> In order to satisfy the criterion respecting comprehensiveness, the health care insurance plan of a province must insure all insured health services provided by hospitals, medical practitioners or dentists, and where the law of the province so permits, similar or additional services rendered by other health care practitioners[164].

Therefore, the *Act* states that medically necessary services offered in hospitals must be provided free of charge. Considering this Canadian infrastructure[165], it is thus the role of

[160] *Canada Health Act*, R.S.C., 1985, c. C-6.
[161] *Ibid* s. 5: "Subject to this Act, as part of the Canada Health Transfer, a full cash contribution is payable by Canada to each province for each fiscal year".
[162] *Ibid* s. 7
[163] André Côté & Bernard Keating, "What Is Wrong with Orphan Drug Policies?" (2012) 15:8 Value in Health 1185.
[164] *Supra* note 160 s. 9.
[165] *Supra* note 129 SS 92(7), (13) and (16).

each province to have programmes and policies, which are approved for drug reimbursement. "The provinces and territories also provide some groups with supplementary health benefits not covered by the Act, such as prescription drug coverage. The level and scope of coverage for supplementary benefits varies between jurisdictions"[166]. Five Canadian provinces, Alberta, British Columbia, Saskatchewan, Ontario, and New Brunswick, have special programs for orphan drug diseases[167]. In order to better understand the legal and policy framework and challenges towards orphan drugs in the provinces of Canada, a detailed view of the situation for specific provinces will be provided. More specifically, we selected four out of five Canadian provinces (Alberta, Ontario, New Brunswick and British Columbia) having specific programs for orphan drugs, in order to analyse and examine the differences and challenges in public health policy concerning orphan drug reimbursement. In contrast, two provinces, Manitoba and Québec, which do not have specific programs for orphan drug diseases will be examined in more detail considering the striking differences in policy mechanisms for drug reimbursement. As a matter of fact, the province of Québec has its own evaluation process for drug reimbursement, whereas the other provinces all rely on the CDR. Furthermore, the province of Québec, having French as an official language, often publishes literature in French that is not always readily accessible to non-French readers, whereas other provinces publish in English. We are thus bringing

[166] Health Canada and the Public health Agency of Canada Government of Canada, "Provincial/territorial role in health", (26 July 2004), online: <http://healthycanadians.gc.ca/health-system-systeme-sante/cards-cartes/health-role-sante-eng.php>. (Accessed April 25 2016)

[167] Devidas Menon, Derek Clark & Tania Stafinski, "Reimbursement of Drugs for Rare Diseases through the Public Healthcare System in Canada: Where Are We Now?" (2015) 11:1 Healthcare Policy | Politiques de Santé 15. This article provides a comprehensive overview of all the programs in Canada regarding orphan drug reimbursement.

together materials in both languages in order to give the current situation on public drug reimbursement programs for rare diseases.

Regarding the basic principles involved in the evaluation of decisions for reimbursement of orphan drugs in Canada and abroad, a recent study provided a qualitative insight on these policies. According to the authors, there are ten basic key points taken into account by "government policy makers or senior staff of agencies" involved in drug review for reimbursement:

- the eligibility aspect with characteristics of the disease and related drugs;
- the patient population;
- the clinical evidence;
- the cost figures for providing the drug;
- the cost effectiveness for the evaluation of the economic aspect;
- the patient and family input for the review process;
- the composition of the review and decision making committee;
- the options for reimbursement considering the availability of choices;
- the factors which are considered in the decisions by the committee;
- a transparent review process as well as final decisions which should be made available to the public[168].

In our view, these key points should be encompassed in all framework and policies regarding orphan drugs to aim at fair and unbiased approaches towards patients suffering from these rare diseases. It is therefore important that all provinces abide by

[168] Hilary Short, Tania Stafinski & Devidas Menon, "A National Approach to Reimbursement Decision-Making on Drugs for Rare Diseases in Canada? Insights from Across the Ponds" (2015) 10:4 Healthc Policy 24 at 28.

these key points to insure equity for all Canadian patients affected with rare diseases. If not, implementation of the neglected elements should be envisioned.

1.2.1 In Alberta

Alberta participates in the national CDR for all new drugs recommendations. There is a list of over 4,000 drugs (Alberta Drug Benefit List), which defines all prescription drugs and drug products that are covered by the ministry's supplemental health plans[169].

There is a specific public program for orphan drug reimbursement that started in 2009. It is called the "Rare Disease Drug Coverage Program"[170] and it is mainly oriented towards patients with lysosomal storage disorders. It is part of an ethical and compassionate governmental support for these rare diseases[171]. The drug plan in Alberta refers to a rare disease as a lysosomal storage disorder with a frequency of less than 1/50,000 Canadians[172]. Lysosomal storage disorders are a group of nearly 50 diseases, which result from the accumulation of substrates in the lysosomes (considered as the digested system of the cell) due to enzyme deficiencies caused by a gene mutation. They present marked phenotypic and genotypic variability, which may lead to severe clinical manifestations. Different therapies are possible, but for a few of these diseases, enzyme

[169] Alberta Health-Government of Alberta, "Alberta Drug Benefit List (ADBL) Alberta Health", online: <http://www.health.alberta.ca/services/drug-benefit-list.html>. (Accessed April 2 2016)
[170] Alberta Health-Government of Alberta "Alberta drug benefit list rare diseases drug coverage, *Section 2: Rare Diseases Drug Coverage Program"*, (2014), Alberta Blue Cross, online: <https://www.ab.bluecross.ca/dbl/pdfs/dbl_sec2.pdf> (Accessed January 24 2015).
[171] Alberta Health-Government of Alberta, Health and Wellness, "Alberta Rare Diseases Drug Program Fact Sheet", December 2008, online: < http://www.health.alberta.ca/documents/Pharma-Strategy-2008-rare-disease.pdf> (Accessed April 2 2016). See also *supra* note 104.
[172] *Supra* note 103.

replacement therapy is the treatment of choice at the present time, which is provided by infusion once a week or every other week depending on the drug administered and the disease involved[173]. The Alberta process for orphan drug reimbursement involves a group of specialists with experience in genetic diseases who review and provide clinical information on rare diseases for individual applications for the rare disease Drug Coverage program for reimbursement of specific drugs according to guidelines previously established. They then provide their counsel and advice to the provincial Expert Committee on Drug Evaluation and Therapeutics (Review Panel)[174]. It is worth mentioning that the Review Panel "must review all drug products not eligible for review by CDR. It provides advice and recommendations to the Minister concerning the therapeutic value and cost-effectiveness of the drugs"[175].

The Minister of Health of Alberta is the person who decides who will have access to the orphan drug under the Alberta government-sponsored program for the treatment of rare diseases[176]. Since April 1 2009, orphan drugs are considered for coverage by the government for the following rare diseases: Gaucher Disease, Fabry disease, Mucopolysaccharidosis Type I (Hurler/Hurler-Scheie diseases), Pompe Disease, Mucopolysaccharidosis type II (Hunter disease).

The initial eligibility criteria are that the patient must have "Alberta government-sponsored drug coverage, have continuously registered in the Alberta Health Insurance Plan for a minimum of 5 years (if the patient is less than 5 years, then the parents must

[173] Joe T R Clarke, "Narrative review: Fabry disease" (2007) 146:6 Ann Intern Med 425.
[174] *Supra* note 171.
[175] Alberta Health-Government of Alberta, "Prescription drug program – Reviews and approvals Alberta Health", online: <http://www.health.alberta.ca/services/drugs-review.html>. (Accessed June 2 2016)
[176] Alberta Human Services Drug benefit Supplement, Section 4, April 2016, Online: <https://www.ab.bluecross.ca/dbl/pdfs/hsdbs.pdf> (Accessed April 2 2016).

respect this 5-year registration), and meet the clinical criteria for the orphan drug on the list"[177]. Afterwards, physicians in charge of patients with one of the aforementioned rare diseases need to complete an application form for each individual, after having advised the patient of the forms to be completed and the process of the coverage program. Forms are then sent to the Alberta Blue Cross who supports the Review Panel. The multi-step process is time consuming and tedious since it involves the evaluation of each application by the Alberta Blue Cross. If the form is complete, it is sent to Alberta Health in order to verify that the patient meets Alberta Health Care Insurance Plan requirement. After confirmation that all requirements are fulfilled, Alberta Blue Cross sends the application to the Review Panel for evaluation. After completion of the evaluation by the Review Panel, Alberta Blue Cross informs the rare disease specialist treating the patient, as well as the patient or parents/legal guardians of the patient, of the decision of the Review Panel. If the decision is positive, the date of approval of the Review Panel will be the start for the orphan drug coverage eligibility, which is accepted for a maximum of one year. It is clearly stated that the approved orphan drug coverage depends on clinical outcomes of the patient. Therefore, monitoring of these clinical outcomes for patients on a regular-basis is required and the coverage of the treatment will cease if the response of the patient is inadequate, or if his clinical situation deteriorates according to the withdrawal criteria established in correlation with an orphan drug and supported by the Review Panel[178].

Importantly, all 12-month renewals of the prescription of the orphan drug necessitate that a new application to the Rare Diseases Drug Coverage program be

[177] *Ibid.*
[178] *Ibid*.

repeated. It is thus the responsibility of the patient (or parents/guardians) and the rare disease specialist to re-apply for the drug coverage before the one-year expiration date. The prescription quantities are also restricted to monthly supplies to avoid wastage of the expensive drugs. It is not possible to ask for supplies of these orphan drugs for a longer period, even for vacation holidays. Moreover, there are standard rules to apply and must be respected if the patient needs to leave the country. The initial process is thus time consuming and labour-intensive considering that a patient might be in need of a rapid treatment. If the clinical outcomes are positive, it is also a burden for the physician to reapply yearly for each of his patients in order to ensure continuation of the treatment.

1.2.2 In Ontario

The Ministry of Health in Ontario has developed an innovative framework approach for orphan drugs in 2007, considering the lack of a national strategy in Canada, called "Drugs for Rare Diseases (DRD)". This approach is an evidence-based clinical strategy also taking into account the needs of patients and the reimbursement costs[179]. A group of clinical and health economic experts were asked by the Ontario Health Ministry to develop "a new evaluation framework" for orphan drugs to receive reimbursement by the province. They worked together to seek the "best available evidence" to predict the benefits or lack thereof of treatment with orphan drugs in patients with rare diseases. This approach allows the identification of a cohort of individuals that may benefit from

[179] Ministry of Health and Long-Term Care Government of Ontario, "Drugs For Rare Diseases (DRD)- Health Care Professionals - MOHLTC", online: <http://www.health.gov.on.ca/en/pro/programs/drugs/how_drugs_approv/review_rare_diseases.aspx>. (Accessed April 2 2016)

treatment with a specific orphan drug and where coverage of the drug might be supported by the province.

In Ontario, there is a Citizen's Council with a mandate to "discuss and respond to questions or topics posed by the Executive Officer. It produces a specific report in answer to these questions or topics"[180]. The Council's report is then sent to the Minister of Health, the Executive Officer, as well as Ontarians (via the Ontario's website), so that this transparency will help people understand the process and opinions discussed. This will be followed by the response of the Executive Officer emphasizing the views of the Ministry on how the recommendations will be implemented. Regarding orphan drugs for rare diseases, the Citizen's Council met in 2010 and provided a report to the Executive Officer on their views and approaches, which have been incorporated in the "DRD review and evaluation framework in Ontario"[181]. It is worth to mention that the Ontario public drug program is the second largest drug insurance program in North America[182].

In 2006, the Ontario government decided to reform the public drug system by initiating the *Transparency Drug System for Patients Act, 2006*[183] which made changes to the *Ontario Drug Benefit Act*[184] and the *Drug Interchangeability and Dispensing Fee Act*[185]. Orphan drugs, as well as all other drugs, will be considered for listing and designation once the pharmaceutical manufacturer has submitted a complete application

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[180] Ministry of Health and Long-Term Care Government of Ontario, "Citizens' Council - Ontario Public Drug Programs - Ministry Programs - Public Information - MOHLTC", online: <http://www.health.gov.on.ca/en/public/programs/drugs/councils/reports.aspx>. (Accessed April 2 2016)
[181] *Supra* note 179.
[182] "Ontario vs. the pharmacists", (22 April 2010), online: *Macleans.ca* <http://www.macleans.ca/news/canada/ontario-vs-the-pharmacists/>.(Accessed April 4 2016).
[183] Provinces and territories, Bill 102, *An Act to amend the Drug Interchangeability and Dispensing Fee Act and the Ontario Drug Benefit Act*, 2nd Sess, 38th Leg, Ontario, 2006 (assented to 20 June 2006)
[184] *Ontario Drug Benefit Act* R.S.O. 1990, c. O.10
[185] *Regulation 935 under the Drug Interchangeability and Dispensing Fee Act* R.R.O. 1990, Reg. 935: GENERAL

to the Ministry of Health and Long-Term Care and is compliant with the *Ontario Drug Benefit Act* and *Regulation 935 under the Drug Interchangeability and Dispensing Fee Act*[186]. Its specific requirements and guidelines are comprised of "template letters, checklists and worksheets" to facilitate the manufacturers' submission process for orphan drugs. The Ministry can always ask the manufacturer for more information throughout the review evaluation. Drugs that are not on the Ontario Drug Benefit (ODB) program list (and no other drug alternatives exist) must follow the path of the Exceptional Access Program (EAP)[187]. This program aims to "facilitate patient access for drugs not funded by ODB. Then, the Committee to Evaluate Drugs (CED), an expert advisory committee from the Ministry, will provide recommendations (according to specific guidelines and policies) to the Executive Officer, who on behalf of the Ministry will decide whether to fund these orphan drugs. The role of the CED is better explained as follows:

> Typically the CED recommends consideration through EAP for drug products where strong clinical evidence is not available to support efficacy and/or cost-effectiveness, when compared to other drugs already funded through the ODB program[188].

The example of one orphan drug called Elaprase® (Idursulfase)[189], given to patients affected with Hunter disease (mucopolysaccharidosis type II), is considered for coverage after its evaluation by the Executive Officer of the Ontario Public Drug

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[187] Ministry of Health and Long-Term Care Government of Ontario, "Exceptional Access Program - Ontario Public Drug Programs - Health Care Professionals - MOHLTC", online: <http://www.health.gov.on.ca/en/pro/programs/drugs/eap_mn.aspx>. (Accessed April 3 2016).
[188] *Ibid*.
[189] Elaprase is manufactured by Shire, a large pharmaceutical company, Shire, "Elaprase.com - What is Elaprase?", online: <http://elaprase.com/about/>. (Accessed April 2 2016).

Programs, because this orphan drug is not listed on the Ontario Drug Benefit Formulary under the EAP. The same process applies for patients affected with the less severe and moderate forms of Gaucher disease type I and for adult and pediatric patients with neurological progressive manifestations of Niemann-Pick type C disease who are treated with Zavesca® (Miglustat)[190], and Naglazyme® (galsulfase) for the treatment of Mucopolysaccharidosis type VI (MPS VI disease).

Another example of an orphan drug, Aldurazyme® (Laronidase)[191] given to patients affected with Hurler disease (Mucopolysaccharidosis type I) has a slightly different access procedure. The reimbursement process must go through the Inherited Metabolic Diseases (IMD) program in order that the drug be evaluated and eventually reimbursed by the Ontario Ministry[192]. Patients must meet specific criteria and be registered in the IMD program in order to be eligible for funding, and the drug must be prescribed by an Ontario physician.

Fabry disease is another lysosomal storage disorder. Briefly, it is an underdiagnosed disease because it presents marked heterogeneity in the phenotype and genotype. Even if it is an X-linked disorder, women can also be affected and sometimes as severely as men[193]. There are two orphan drugs reimbursed by the Ministry in

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[190] Zavesca, is given to patients orally and is manufactured by Actelion. "ZAVESCA® [miglustat] Capsules, 100mg", online: <https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=19754>. (Accessed April 2 2016)

[191] Aldurazyme is manufactured by Genzyme, A Sanofi Company, a large pharmaceutical company

[192] Ministry of Health and Long-Term Care Government of Ontario, "Public Drug Programs Aldurazyme® (laronidase) – Mucopolysaccharidosis Type I (MPS I) Reimbursement Guidelines Version 1 – October 2011", online: <http://health.gov.on.ca/en/pro/programs/drugs/how_drugs_approv/docs/aldurazyme_reimb_guide.pdf >(Accessed April 4 2016).

[193] *Supra* note 173.

Ontario. One is Fabrazyme® (agalsidase beta from Genzyme, a Sanofi Company)[194] and the other is Replagal® (agalsidase alfa from Shire)[195]. Both drugs are infused biweekly. The process of reimbursement is different for these two drugs, since in September 2013, it was transferred from the University Health Network (UHN) to the Ontario Public Drug Programs (OPDP). In Canada, there is a long-term research project called the "Canadian Fabry Disease Initiative (CFDI)" to evaluate Fabry patients since 2006[196]. Therefore, the CFDI has been given the mandate to "continue to assess new patient applications, annual renewals, and manage the ordering of enzyme replacement therapy (ERT) from the manufacturers"[197]. The CFDI has strict evidence-based treatment guidelines for patients to be admissible for ERT in Canada[198].

Since 2015, a new program designed for Ontario patients who have their closest physician either in Manitoba or in Québec, now have access to the Provincial Borders Drug Program (PBDP), which is a public drug program for ODB Program clients who require access to EAP products[199]. Physicians who are licensed either by the Collège des médecins du Québec or the College of Physicians and Surgeons of Manitoba may submit funding requests on ODB patients for an EAP product, with the relevant clinical information and rationale for the application.

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[194] Fabrazyme® is an enzyme replacement therapy drug provided by infusion to Fabry patients at 1.0 mg/kg weight every 2 weeks, Genzyme, "Fabrazyme", online: <https://www.fabrazyme.com/>. (Accessed April 5 2016).
[195] Replagal® is an enzyme replacement therapy drug provided by infusion to Fabry patients at 0.2 mg/kg weight every 2 weeks, "Shire: List of Products & Therapies", online: <https://www.shire.com/products/product-list>. (Accessed April 5 2016).
[196] S M Sirrs et al, "Outcomes of patients treated through the Canadian Fabry disease initiative" (2014) 111:4 Mol Genet Metab 499. doi: 10.1016/j.ymgme.2014.01.014.
[197] Michael L. West et al. "Canadian Fabry Disease Treatment Guidelines 2012" Halifax, online: <http://www.garrod.ca/wp-content/uploads/Canadian-FD-Treatment-Guidelines-2012.pdf> (Accessed April 6 2016).
[198] *Ibid*.
[199] *Supra* note 187.

Ontario has also a Compassionate Review Policy for life-, limb- or organ-threatening conditions under rare circumstances where the Executive Officer will consider requests for drugs in the absence of a final funding decision under special criteria, namely no other alternatives through the EAP, or because the patient failed all appropriate non-pharmacological alternatives[200].

The Citizen's Council has played an important role in representing the public's view in a report on topics posed by the Executive Officer. The report is then taken into account by the Ministry, and in the case of rare diseases, it provided a compassionate aspect for affected individuals. This is a good endeavour on the part of the Ontario Ministry to listen to its constituents. The orphan drug policies in Ontario have been updated regularly. Nevertheless, it remains a complex program for patients to have access to and for physicians to fill out the administrative documents over time for each patient.

1.2.3 In New Brunswick

Certain orphan drugs are reimbursed in New Brunswick for specific rare diseases, mostly lysosomal storage disorders. The coverage plan is in partnership with Ontario with the DRD framework in order to review orphan drug applications with the best available evidence. Therefore, the DRD plan in New Brunswick refers to the same drugs as in Ontario and the requests submitted by physicians in New Brunswick are evaluated by the external medical experts from the Ontario Public Drug program with the same clinical criteria. Eligibility criteria are that patients must be permanent

[200] *Ibid*.

residents of New Brunswick and have a Medicare Card[201]. The coverage plan is for the following diseases: Aldurazyme® (laronidase) for the treatment of Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I); Elaprase® (idursulfase) for the treatment of Hunter's Syndrome; Ilaris® (canakinumab) for the treatment of Cryopyrin-Associated Periodic Syndrome (CAPS); Myozyme® (alglucosidase alfa) for infantile/early and adult/late onset Pompe disease, Naglazyme® (galsulfase) for the treatment of Mucopolysaccharidosis type VI (Maroteaux-Lamy, MPS VI) [202] and Zavesca® (miglustat) for the treatment of Niemann-Pick Type C (NPC) disease.

1.2.4 In Manitoba

In Manitoba, all drugs must firstly be approved by Health Canada. Afterwards, there is a standard review procedure through the national CDR and the Manitoba Drug Standards and Therapeutics Committee (MDSTC)[203]. It is worth noting that Manitoba is an active member of the CDR[204]. Therefore, a new drug (or combination of drugs) needs to be filed with the CDR Directorate. The MDSTC is an autonomous group selected by the Minister of Health upon recommendations by the College of Physicians and Surgeons of Manitoba, Doctors Manitoba, the Manitoba Pharmaceutical Association, and the University of Manitoba. This Committee is thus sovereign from the government,

[201]Government of New Brunswick, "New Brunswick Drugs for Rare Diseases Plan", (08:44:39.0), online: <http://www2.gnb.ca/content/gnb/en/services/services_renderer.201352.New_Brunswick_Drugs_for_Rare_Diseases_Plan.html>. (Accessed April 4 2016).

[202] Naglazyme (galsulfase) is an enzyme replacement therapy drug provided by infusion to patients affected with MPS VI. The drug is manufactured by BioMarin Pharmaceutical Inc, "About NAGLAZYME", online: <http://www.naglazyme.com/about-naglazyme/>. (Accessed April 4 2016).

[203] Government of Manitoba "Drug Formulary Review Process | Manitoba Drug Benefits and Interchangeability Formulary | Manitoba Health, Seniors and Active Living | Province of Manitoba", online: <http://www.gov.mb.ca/health/mdbif/review.html>. (Accessed April 5 2016).

[204] Therapeutics Initiative "[61] What is the Common Drug Review?", (31 December 2006), online: <http://www.ti.ubc.ca/2006/12/31/what-is-the-common-drug-review/>. (Accessed April 4 2016).

and is comprised of six health care professionals (three physicians and three pharmacists) who propose "recommendations on drug interchangeability and on the therapeutic and economic value of drug benefits"[205]. A manufacturer who wants his new drug to be accepted for drug coverage must submit the drug application to the MDSTC. This latter Committee will consider the recommendations of the CDR, but also take into account recent scientific publications, similar drugs, expected cost, and benefits for the health of patients before making a recommendation for benefit listing. In order for a drug to be considered for listing on the Manitoba Formulary, a utilization management agreement (UMA) must be signed:

> The UMA provides a statement of the benefit of the product as compared to currently listed products, as well as cost impact projections, assurances of appropriate promotion and provision for health outcomes research[206].

Finally, the Manitoba Minister of Health, after reviewing the recommendations from the MDSTC, the health review from Manitoba and the signed UMA gives the final approval for benefits under the Pharmacare drug benefit program. The Minister will then sign the Specified Drug Regulation and the Manitoba Drug Benefits and Interchangeability Formulary. Pharmacare is comprised of three parts. The 3rd part of Pharmacare is dedicated to Exception Drug Status (EDS) coverage which is specific for each patient regarding his particular clinical situation. The patient's physician must apply for the provincial coverage of these drugs. Reapplication each year for the same

[205] *Supra* note 203.
[206] *Supra* note 203.

orphan drug is necessary[207]. Also, recommendations are formulated by the MDSTC. Orphan drugs are part of EDS and must meet strict criteria before being reviewed. One of these criteria is that the drug is prescribed:

> […] because it is required in the diagnosis or treatment of an illness, disability, or condition rarely found in Manitoba. Evidence, including therapeutic and economic evidence, provided to the Minister in accordance with the criteria established by him or her, supports a specific treatment regime which includes use of the drug or other item[208].

Again the process in Manitoba for orphan drug reimbursement is time-consuming and involves substantial bureaucracy for the physician involved in treating rare disease patients.

1.2.5 In Québec

Similar to all provinces, all drugs must be approved by Health Canada for its commercialization, thus respecting the efficacy, safety and quality of drugs. Contrary to other provinces who rely on CDR, Québec has its own evaluation process for reimbursement with the "Institut national d'excellence en santé et en services sociaux" (INESSS)[209]. It is noteworthy to mention that only medications which are part of the Régie d'assurance maladie du Québec (RAMQ) [210] are covered by the Prescription Drug

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[207] "Drug Benefit Programs", online: <http://www.drugcoverage.ca/en-ca/Provincial-Coverage/manitoba/drug-benefit-programs>. (Accessed April 4 2016)
[208] *Supra* note 203.
[209] *Loi sur l'Institut national d'excellence en santé et en services sociaux, chapitre I-13.03*, Online: https://www.inesss.qc.ca/fileadmin/doc/INESSS/DocuAdmin/Lois_Politiques/Loi_INESSS.pdf (Accessed April 5 2016).
[210] *An Act respecting the Régie d'assurance maladie du Québec*, CQLR, chapter R-5.

Insurance plan, which was devised in 1997 for the needs of the health of the population of Québec[211]:

> The purpose of the basic plan is to ensure that all persons in Québec have reasonable and fair access to the medication required by their state of health.
> To that end, the plan provides for a minimum level of coverage for the cost of pharmaceutical services and medications, and requires a financial participation on the part of persons or families covered by the plan depending, in particular, on their economic situation[212].

Needless to say that the RAMQ, under the authority of the Minister of Health and Social Services, "administers the public health and prescription drug insurance plans: it informs the public, manages the eligibility of persons, remunerates health professionals and ensures the secure flow of information[213]". Everyone in Québec must be covered by the Prescription Drug Insurance pl*an* which can either be private or public[214]. INESSS must provide an updated list of medications according to section 60 of the Prescription Drug Insurance plan[215].

The process (see Summary of process for the registration of a medication on the RAMQ list in Figure 8) begins with the drug manufacturer submitting an application containing all pertinent information concerning studies performed by its company. INESSS will then evaluate this application and rely on other complementary studies

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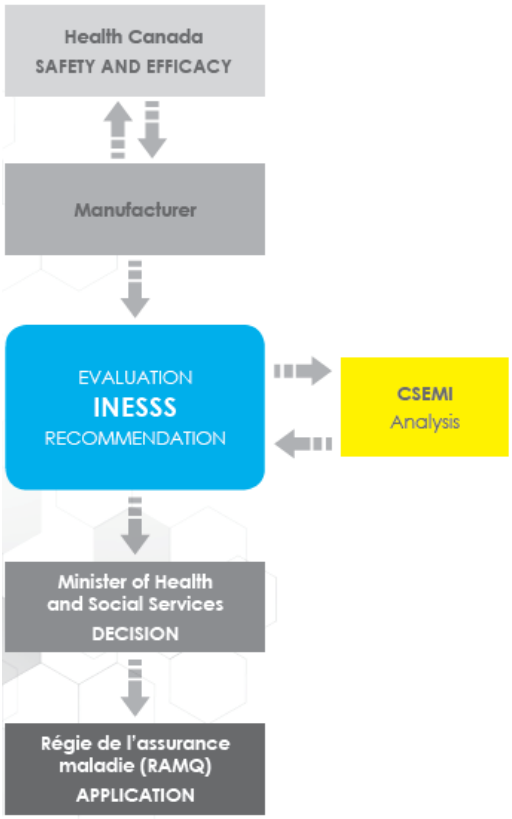
[211] *Act Respecting Prescription Drug Insurance* (RSQ, ch. A-29.01), s. 1.
[212] *Ibid*. s. 2. It is important to highlight the fact that this article mentions that only a minimum level of coverage for the cost of pharmaceutical services and medications is covered by the plan leading to a major dichotomy with orphan drugs for rare diseases.
[213] Régie de l'assurance maladie du Québec, Government of Québec, "Mission | RAMQ", online: <http://www.ramq.gouv.qc.ca/en/regie/Pages/mission.aspx> (Accessed April 6 2016); See also *supra* note 210.
[214] *Supra* note 211, ss. 15,15.1,16-18,78.
[215] Ibid, s. 60; *Regulation respecting the list of Medications covered by the basic prescription drug insurance plan*, CQLR c A-29.01, r 3.

during the process. If the application is judged to be receivable, INESSS inscribes a worksheet with the medication to be evaluated on its website for 30 days in order to receive comments from patients, health professionals, and the population in general. All comments are provided to the members of the Scientific Committee called "Comité scientifique de l'évaluation des médicaments pour des fins d'inscription" (CSEMI) who will proceed with the evaluation. All drug applications are evaluated by professionals at INESSS and also by the Scientific Committee. This Committee is comprised of physicians/clinicians, pharmacists, ethicists, managers and members of the general public, as well as pharmacoeconomists. Often, external expertise is requested. INESSS's analysis is based on the following criteria:

> (1) the reasonableness of the price charged;
> (2) the cost-effectiveness ratio of the medication;
> (3) the impact that entering the medication on the list will have on the health of the general public and on the other components of the health and social services system; and
> (4) the advisability of entering the medication on the list, given the purpose of the basic prescription drug insurance plan[216].

[216] *Supra* note 209 s.7.

Figure 8. Summary of the Process for the Registration of a Medication on the RAMQ List[217].



Source: INESSS

After a rigorous evaluation, the Committee provides its recommendations to the Board of directors at INESSS, and then to the Minister who decides whether to approve the updated list:

> […] Only a medication from a manufacturer accredited by the Minister may be considered for entry on the list. However, the Minister may enter on the list the medication of a manufacturer who has not been granted accreditation

[217] Institut national d'excellence en santé et en services sociaux Government of Québec, "INESSS: Evaluation process and criteria", online: <https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Processus/Evaluation-medic_EN_28082013.pdf>. (Accessed April 6 2016).

if the medication is unique and essential. […][218].

The *List of Medications* comprises exceptional medications, such as orphan drugs, "for which coverage is provided under the basic plan only in the cases, on the conditions or for the therapeutic indications determined in the regulations of the Minister and therefore, recognized by INESSS. These conditions may vary depending on whether coverage is provided by the RAMQ or under a group insurance or an employee benefit plan"[219]. Certain drugs for rare diseases are on the list of exception drugs (médicaments d'exception) administered by the RAMQ which gives the right to reimbursement. These drugs must also meet very specific criteria. Physicians wishing to prescribe exception drugs can do it through a specific code. It appears that for all persons who are covered by the RAMQ, the number of prescriptions of "médicaments d'exception" went from 342,866 in 1998 to 8,6 million in 2010, generating an increasing cost by the RAMQ from 32 to 623 million Canadian dollars[220]. Therefore, between 1998 and 2010, there was a substantial increase of approximately 1500%, which was higher than the 200% growth of drug expenditure for that same period of time[221].

If one or more drugs are not featured on the *List of Medications*, there is also a program called "Patient d'exception", which allows under exceptional circumstances, patients to have reimbursement of drugs. This program is considered as a last resort for debilitating medical conditions significantly affecting the health of a patient. In order to

[218] *Supra* note 211, s. 60.
[219] Institut national d'excellence en santé et en services sociaux, Government of Québec, "INESSS: Exceptional Medications", online: <https://www.inesss.qc.ca/en/activities/drug-products/evaluation-process-and-criteria/exceptional-medications.html>. (Accessed April 4 2016)
[220] Mélanie Bourassa Forcier, *Projet de viabilité - Contrat pour l'accès aux médicaments et pour l'innovation au Québec (CAMI),* CIRANO Project Reports*,* Centre Interuniversitaire de Recherche en Analyse des Organisations (CIRANO), (2014) at 16
[221] *Ibid*.

benefit from the program, the attending physician must fill an authorization request. The expert committee in pharmacy of the RAMQ then evaluates the request on the basis of specific criteria[222]. Over the years, there also seems to have an increase in cost for "Patient d'exception". In 1998, the cost was $1,000,647 for 3,625 patients whereas it $53,554,155 for 13,975 patients in 2009[223]. It seems that there is an increased need for programs such as "Patient d'exception". However, the RAMQ can still refuse an authorization for a specific drug. The patient may then ask for a revision while providing new elements to consider, or if it does not suffice, the decision can be upheld at the "Tribunal administratif du Québec"[224].

Nevertheless, an innovative report published in 2012 suggested possibilities for governmental authorities, public insurers, to conclude "Product Listing Agreements (PLA) with pharmaceutical companies in order to reduce clinical and/or financial uncertainties regarding reimbursement of drugs"[225]. In November 2011, a pilot project suggested by INESSS to evaluate the possibilities of such an agreement was done with three anti-cancerous drugs. INESSS's conclusions submitted to the Ministry of Health after thorough evaluation of this pilot project showed an opening for future risk sharing agreements between the government and pharmaceutical companies[226]. It should be noted that financial agreements between the Minister of Health and Social Services and

[222] *GG c Québec (Régie de l'assurance maladie du Québec)*, 2010 QCTAQ 06450.
[223] *Supra* note 220 at 17-18
[224] Institut national d'excellence en santé et en services sociaux Government of Québec, "Patient d'exception | RAMQ", online: <http://www.ramq.gouv.qc.ca/fr/professionnels/medecins-omnipraticiens/medicaments/medicaments-patient-exception/Pages/patient-exception.aspx>.(Accessed April 5 2016); *M.R. c. Régie de l'assurance maladie du Québec*, 2006 C, CanLII 74661 (QC TAQ); *HD c. Québec (Régie de l'assurance maladie)*, 2013, CanLII 19946 (QC TAQ); *G.J. c. Québec (Régie de l'assurance-maladie du Québec)*, 2004 C, CanLII 66734 (QC TAQ)
[225] Mélanie Bourassa Forcier, *Ententes entre gouvernements et compagnies pharmaceutiques* (Montréal, Québec: CIRANO, 2012).
[226] *Ibid* at 25.

pharmaceutical companies are made possible according to the *RAMQ*[227], whereas clinical agreements would be possible for medications provided in hospitals according to the *Loi sur les services de santé et services sociaux*[228].

A specific mandate was given to INESSS in 2010 in Québec to establish a strategy for the management of rare diseases[229]. During the same year, the Minister of Health and Social Services, Yves Bolduc stated during the congress for the "Regroupement québécois pour les maladies orphelines" (RQMO):

> Quand on devient malade, on n'en est pas responsable, surtout quand c'est une maladie génétique. Les Québécois et Québécoises ont le droit de recevoir les traitements qu'il leur faut, quelle que soit leur maladie. Comme société, on est capable de l'assumer: ce sont des maladies rares, les traitements coûtent plus cher, mais il y en a moins. C'est une question d'équité [230].

At the same time, a committee was supposed to be implemented to work on strategies for rare disorders in Québec. Unfortunately, this committee never saw the light of day. It seems that nothing has changed in the last 6 years regarding strategies for orphan diseases and treatment with orphan drugs. The process to access orphan drugs is still the same in Québec and there is no improvement to make it simpler for patients with rare diseases and their physicians.

[227] *Supra* note 210 s. 52.1.
[228] *Act respecting health services and social services,* c. S-4.2, s. 118.
[229] *Supra* note 26
[230] *Ibid* at 3.

1.2.6 In British Columbia

British Columbia has a general reimbursement drug process called BC Pharmacare. Orphan drugs are part of a special program under the authority of the "Expensive Drugs for Rare Disease Advisory Committee (EDRD)," with a role to provide recommendations to the Minister of Health about reimbursement. EDRD is a multidisciplinary committee comprised of doctors, pharmacists, ethicist, health economics and representatives from provincial drug plan. The Minister has the final decision about reimbursement of these orphan drugs[231].

In practice, and as discussed with a BC physician treating patients affected with rare diseases, it is a complicated process in that none of the drugs are listed on the provincial formulary other than Myozyme for infantile Pompe disease (not late onset), which means they are not reimbursed for all cases. However, all the drugs, except the Morquio IVA drug, are being reimbursed through the provincial EDRD program. There are treatment guidelines (basis of criteria) for all drugs and if a physician brings a patient to the committee, they are reviewed using those guidelines, and then the committee makes a recommendation to the province as to whether or not they should funded. This allows physicians to still advocate even if the patient is not likely to benefit from the treatment. This removes the physician from the need to be a gatekeeper. Most of all, the committee recommends to fund and the province then funds. The cases that were turned down by the committee were all cases that wouldn't have benefited from therapy. The process works well although it generates extensive paperwork. It seems that the BC

[231] *Supra* note 167.

process is well accepted by involved physicians due to this mechanism which allows both advocacy and reason at the same time. At the present time, CFDI Fabry disease patients do not go through this committee, but likely will in the future considering they are treated on the basis of criteria.

1.2.7 Inequities between Provinces for Rare Disease Coverage

Pompe disease is a rare lysosomal storage disorder due to an enzyme deficiency leading to accumulation of glycogen in the lysosomes in body cells. The clinical manifestations of the disease lead to a broad spectrum with progressive muscle weakness, with an eventual loss of muscle function, respiratory and heart problems causing death[232]. The incidence is about 1/40,000 and is characterized by marked phenotypic and genotypic heterogeneity. Treatment is possible with enzyme replacement therapy of the drug Myozyme® (Genzyme, a Sanofi Division) infused every two weeks.

This disease has recently been the subject of recent media attention because it affected two brothers living in different Canadian provinces: one brother, who is 64 years old, lives in Manitoba where government reimbursement of Myozyme is possible, and his brother, who is 61 years old, lives in British Columbia (BC) where the drug is not covered by the BC Health system[233]. The cost of Myozyme may reach $600,000 CAD per year/patient. The brother who lives in British Columbia has stated that the

[232] Barry J Byrne et al, "Pompe disease: design, methodology, and early findings from the Pompe Registry" (2011) 103:1 Mol Genet Metab 1. doi: 10.1016/j.ymgme.2011.02.004.
[233] Ben Spurr, "Inequities between provinces in treating rare diseases | Toronto Star", *thestar.com*, online: <https://www.thestar.com/news/canada/2016/02/08/inequities-between-provinces-in-treating-rare-diseases.html>. (Accessed April 20 2016).

system is unfair because the same type of treatment should be offered in both provinces. A spokesperson from the Ministry of Health in British Columbia would not comment on this specific case but stipulated that "the Ministry considers requests to cover Myozyme on an exceptional last-resort, case-by-case basis" and that some patients have received coverage of the drug[234]. The Manitoba government has stated that at least five persons affected with Pompe disease have received full reimbursement of Myozyme. The lack of consistency in the reimbursement programs throughout Canada is a major issue considering the consequences on the health of Canadian citizens affected with rare diseases. Such inequities may be encountered with patients having to move from one province to the other.

A similar case emerged in relation to cystic fibrosis and the orphan drug Kalydeco® (ivacaftor) with a cost of $1,600 a day per affected patient. Alberto Galina, the project director of Million Dollar Meds, a collaborative synergy between the University of British Columbia's graduate school of journalism and the school's pharmaceutical sciences department, has investigated the reimbursement of this drug which is accepted in BC but not in Ontario[235]. The disparity between provinces and the lack of a national framework has led to inequities among Canadian citizens. Table 2 shows drugs for rare diseases for different provinces and their provincial coverage as part of a general reimbursement process. Moreover, we would like to emphasize that some of these drugs are accepted on a case-by-case basis by provinces according to their own conditions.

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[234] *Ibid.*

[235] CBC News British Columbia, High drug prices for rare diseases subject of UBC journalism project, Feb 29 2016, online: <http://www.cbc.ca/news/canada/british-columbia/drug-prices-rare-diseases-1.3470028> (Accessed April 15 2016).

Table 2. Drugs for Rare Diseases for Different Provinces and their Provincial Coverage as Part of General Reimbursement Processes.

Drugs	Alberta	Ontario	New Brunswick	Manitoba	Quebec	British Colombia
Fabrazyme®*	✔	✔	✖	✖	✖	✖
Replagal®*	✔	✖	✖	✖	✖	✖
Elaprase®	✔	✔	✔	✖	✖	✖
Zavesca®	✖	✔	✔	✖	✖	✖
Aldurazyme®	✔	✔	✔	✖	✖	✖
Ilaris®	✖	✔	✔	✖	✖	✖
Myozyme®	✔	✔	✔	✖	✔	✖
Soliris®	✔	✔	✖	✔	✖	✖
Naglazyme®	---	✔	✔	---	---	---
*According to the CFDI criteria						

✓: Covered by the province; X: Not covered by the province; ---: No information found

Source: Our analysis

According to the universality criterion for the health system in Canada, all insured residents are entitled to the same level of health care, on uniform terms and conditions, to the publicly funded health services covered by the provinces[236]. Will there be a uniformity in the availability and accessibility of orphan drugs across Canada? Will the treatment of a life-threatening disorder be discontinued because the orphan drug is not reimbursed in a specific province? Will the patient have to go through a Kafkaesque bureaucracy to have his medication reimbursed despite the delays and the major risks on his health? One must conclude that inequities arise due to different orphan drug strategies for each province, as well as different reimbursement policies, and in the end, different treatment options for patients.

[236] "The Health of Canadians: The Federal Role - Final Report", online: <http://www.parl.gc.ca/content/sen/committee/372/soci/rep/repoct02vol6part7-e.htm>. (Accessed June 4 2016)

2. What Has Been Done About Orphan Drugs Elsewhere

Even in 2016, Canada is still reluctant to address problems regarding orphan drugs. Indeed, considering the striking need for financial support in research regarding rare diseases, there is limited interest for pharmaceutical companies to invest in R&D in Canada[237]. Furthermore, differences between provinces in terms of drug reimbursement have generated discrepancies for Canadians to have access to orphan drugs. On the other hand, some countries have developed policies to address the same issues decades ago. The US, Japan, Australia and the European Union (EU) were proactive in adopting specific legislation for orphan drugs. The focus of this work will be mainly on orphan drug policies developed by the US and the EU.

2.1. The US *Orphan Drug Act*

The US were pioneers in creating a legal framework in the subject of orphan drugs. The efforts to legislate Orphan drugs took a faster turn when media started to reveal the exasperation of patients who, due to market demands, were seeing their last therapeutic resort held hostage[238]. This media frenzy was brought to the attention of the famous television actor Jack "Quincy" Klugman by his brother, Maurice Klugman[239]. In 1981, Maurice, a writer who himself suffered from a rare cancer, wrote an episode of "Quincy" about Tourette's syndrome and the orphan drug problems[240]. Tourette's syndrome (TS) is a neurological chronic disorder with early symptoms occurring in

[237] *Supra* note 49.
[238] Asbury*, supra* note 9 at 111.
[239] Joshua Green, "Jack Klugman's secret, lifesaving legacy", *The Washington Post* (25 December 2012), online: <http://www.washingtonpost.com/blogs/wonkblog/wp/2012/12/25/jack-klugmans-secret-lifesaving-legacy/>. (Accessed June 4 2016)
[240] Quincy, M.E. Jeffrey Hayden, Season 6, episode 14, *Seldom Silent, Never Heard* (1981).

childhood characterized by involuntary movements and repetitive vocal tics[241]. One of the treatments for TS is Pimozide, a neuroleptic drug often used to treat psychiatric disorders. TS was at the forefront of the media because it was not available in the US but available in Canada in 1980[242]. At this time, Representative Henry Waxman (D) of California, chairman of the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, invited Jack Klugman to testify before the US Congress in order to build momentum for a bill. The hearing was held in the upcoming days after the "Quincy" broadcasting of the orphan-drug episode. Jack Klugman did as he had done in the episode, arguing on behalf of legislation for orphan drugs. In fact:

> […] in a brilliant instance of life imitating art, Klugman took industry and government to task in full public view before a crowded press section and television cameras. Federal and industry orphan-drug efforts immediately began to speed up. Before this dramatic stimulant to public awareness of orphan drug problems, however, much had transpired to lay a foundation for action"[243].

Even if the Waxman bill sailed through the House, it had very little chance to pass the Senate since a number of key senators were opposed to the tax credit provision. Klugman and his "Quincy" team then wrote another episode about orphan drug legislation, which aired at the time the bill was being examined by the Senate. This time, the episode featured a fictitious heartless senator, who was deferring an orphan drug bill. Quincy confronted the heartless senator in his office while showing him, out the window, more than 500 patients affected with rare diseases marching toward the Capitol

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[241] "Tourette Syndrome Fact Sheet", online: <http://www.ninds.nih.gov/disorders/tourette/detail_tourette.htm>. (Accessed June 4 2016)

[242] Matthew Herder, "When Everyone Is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada" (2013) 20:4 Accountability in Research 227.

[243] Asbury, *supra* note 9 at 112.

and having signs such as "We Want the *Orphan Drug Act*"[244]. The "Quincy" episodes made a positive difference in the debate since, it seems that Klugman's appearances and dedication were the single most significant catalyst to stimulate public policy in the whole orphan drug saga[245].

Thanks to Klugman and the National Organization for Rare Disorders (NORD), a federal voluntary health organization, on January 4 1983, President Ronald Reagan signed the *Orphan Drug Act* creating incentives for pharmaceutical manufacturers to develop drugs for rare diseases. The *Orphan Drug Act* of 1983 provided tax and market incentives, however it only applied to drugs and biologicals[246]. At the time, the strategy behind the legislation in order to receive an orphan designation was that: "[…] there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug"[247].

2.1.1 Incentives Provided by the *Orphan Drug Act*

Sponsors who, under FDA guidelines, precisely requested and were granted an orphan designation could receive incentives provided by the *Act*. It then received a seven-year period of marketing exclusivity effective on the date of FDA approval. This being said, multiple sponsors could receive designation for the same orphan drug (same condition). However, on a first come, first served basis, it was implemented that just the first sponsor received exclusive rights to market the orphan drug and only after the

[244] Quincy, M.E. Georg Fenady, Season 8, episode 3, *Give Me Your Weak* (1982).
[245] Asbury*, supra* note 9 at 125.
[246] *Orphan Drug Act, supra* note 18.
[247] *Ibid* s. 526(2).

seven-year period has expired can another version of the same drug be approved by the FDA (that also included generic applications). The pharmaceutical company could also receive, as a general rule, a tax credit "for the taxable year an amount equal to 50 percent of the qualified clinical testing expenses for the taxable year[248]". There were also incentives in terms of research grants each year for expenditure of four million US dollars for clinical testing of orphan treatments. Initially, the ODA had not defined a US prevalence for what it considered as a rare disease. The closest description of a type of rare diseases or conditions was stated by the Congress and found in Section 1(b)(1):

> there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States;[249]

Congress already recognized the small number of individuals as a challenge. In order to designate a drug as an orphan drug and implement Section 526 of the ODA, the interim guidelines were decided with a prevalence of less than 100,000 people in the United States[250]. There were discussions, later on, whether to include a definition for "rare disease" in the ODA instead of guidelines. Advocacy groups raised public concerns to increase the number of orphan drugs covered for rare diseases. It was then agreed by the Congress, under the Amendments of 1984, to clarify for pharmaceutical companies, the approval by the FDA of the designation of an orphan drug[251]. Rare disease or condition was defined as "which (A) affects less than 200,000 persons in the United States, or (B)

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[248] *Ibid* at 44H.
[249] *Ibid* at s.1(b)(1).
[250] Asbury, *supra* note 9 at 180.
[251] Li-Hsien Rin-Laures and Diane Janofsky, Recent developments concerning the orphan drug act- Harvard Journal of Law & technology, Vol 4, Spring Issue 1991.

affects more than 200,000 in the United States and for which"[252] "there is no reasonable expectation that the sales of the drug treatment will recover the costs"[253]. Throughout the years, a number of incentive mechanisms and initiatives have been implemented to improve the initial *Act*. In 1990, an effort by the Congress to pass legislation to differentiate orphan drug development from others in terms of commercial value was vetoed by President Bush[254]. In 1992, Congress continued to support incentives for orphan drug and biologic product review by waving the filing fees[255]. In 2002, the *Rare Disease Act*[256] and *Rare Disease Orphan Product Development Act*[257] were signed into law. The NIH Office of Rare Diseases (now the Office of Rare Diseases Research) was given the mandate "to support regional centers of excellence for clinical research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare disease"[258]. Since 1983, the US orphan drug model succeeded in developing and marketing rare diseases for more than 400 drugs and biologic products, whereas only 10 products were approved before that[259]. Arguments against the ODA after its implementation were not frequent. In fact foreign countries have tried to emulate it[260].

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[252] *Health Promotion and Disease Prevention Amendments*, Pub. L. No. 98-551, 98 Stat. 2817 (1984)
[253] *Ibid*.
[254] Sumin Kim, "The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity", 11 Nw.J. Tech. & Intell. Prop. 541 (2013). online: <http://scholarlycommons.law.northwestern.edu/njtip/vol11/iss6/3> (Accessed June 4 2016)
[255] *Supra* note at 24.
[256] US, Bill HR 4013, *Rare Disease Act of 2002,* 107th Cong, 2002, (enacted).
[257] US, Bill HR 4014, *Rare Disease Orphan Product Development Act of 2002,* 107th Cong, 2002, (enacted).
[258] *Supra* note 42.
[259] U.S. Food and Drug Administration, Office of the Commissioner, "Developing Products for Rare Diseases & Conditions", online: <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm>. (Accessed May 27 2016)
[260] Japan implemented a regulation similar to the Orphan drug Act in 1993. *Supra* note 42.

Furthermore, patient access to orphan drugs has hardly been denied[261]. That said, the law is far from perfect and brings its own problems and caveats.

2.1.2. The US Reimbursement Procedure

Although the access to orphan drugs has hardly been denied, the reimbursement procedure in the US is another matter. Payers have no distinct reimbursement process for orphan drugs compared to non-orphan drugs. As a result, the pattern for coverage plans differs greatly from one orphan drug to the other. Payers have traditionally accepted to reimburse orphan drugs without considerable restrictions[262]. However, due to the high prices of orphan drugs, payers have transitioned from fixed co-payments per prescription to co-insurance leaving the cost burden to patients[263]. "Medicaid coverage and reimbursement policies for orphan drugs vary from state to state. Medicare patients seeking orphan drugs face limitations on reimbursement and potentially high out-of-pocket costs"[264]. In the US, patients affected with rare diseases are consequently seeking for Patient-assistance programs offering financial assistance in order to afford their orphan drugs[265]. It seems that management tactics that payers apply, such as co-insurance, are not only for orphan drugs but for non-orphan drugs as well -creating general concerns to ensure patient access.

[261] Rebecca Hyde & Diana Dobrovolny, "Orphan drug pricing and payer management in the United States: are we approaching the tipping point?" (2010) 3:1 Am Health Drug Benefits at15.
[262] Chris Wilson, "Market access procedures for orphan drugs" in *Orphan Drugs* (Elsevier, 2013) 247 at 259 doi: 10.1533/9781908818393.
[263] *Ibid*.
[264] *Supra* note 261 at 20.
[265] *Supra* note 262.

2.1.3. The Salami Slicing Effect

While the ODA created opportunities in research and drug development, pharmaceutical companies also exploited marketing strategies to increase profit. A good example is salami slicing, which "has to do with taking a drug for a particular indication that does not qualify for orphan drug designation and slicing that indication into a number of narrower ones which do qualify. Thus, a manufacturer may be able to obtain broad, but unwarranted, exclusivity for its drug"[266].

The salami slicing effect for drug development approach also implies that:

> […] companies target "rare subsets of common diseases to acquire orphan status for many similar indications for a single drug. In doing so, companies can profit from a larger patient population while retaining orphan drug incentives, but without providing a commensurate increase in patient access to rare disease treatments[267].

An example of a stratification of a disease is breast cancer, which is not considered a rare disease[268]. In fact, it is a practical example of the salami effect since researchers have recently found a rare subset of breast cancer patients, and these patients respond differently to cancer treatment approaches[269]. The authors suggest that patients be stratified into subtypes according to alterations in the genome which might lead to increase efficacy of therapy and a better understanding of the pathophysiology of the disease. The treatment for this rare subset of breast cancer patients can therefore qualify

[266] Patricia J. Kenney. "The Orphan Drug Act - is it a barrier to innovation? Does it create unintended windfalls?" Food Drug Law J, (1988) 43, 669.
[267] Westerly Luth, Sarah Ali-Khan, Tania Bubela, "Canada's Orphan Drug Framework: Lessons from the United States, Europe and Japan", PACEOMICS, Oct. 2015, at 6, online: <http://paceomics.org/wp-content/uploads/2015/10/Canadas-Orphan-Drug-Framework.pdf> (Accessed June 4 2016)
[268] *Supra* note 35 at 758.
[269] Brian D Lehmann & Jennifer A Pietenpol, "Identification and use of biomarkers in treatment strategies for triple-negative breast cancer subtypes" (2014) 232:2 J Pathol 142. doi:10.1002/path.4280.

for an orphan drug designation since it meets the criteria.

A second issue arising from the salami slicing effect regards a drug having indications for both rare and common diseases. A clever marketing strategy would be for the pharmaceutical company to obtain the designation for the orphan drug in the first instance in order to profit from all the incentives offered, and afterwards, market the drug for common diseases[270]. Unfortunately, patients affected with common diseases will not receive the drug at the same time as those with rare diseases, which presents a major ethical problem. The strategy being that companies will first benefit from the orphan drug incentives authorized by the ODA, and when the designation is accepted, companies will apply for the larger market.

As often said: "Nothing is perfect". The ODA has increased the number of marketed orphan drugs for American citizens over the years. On the other hand, it has also paved the way for clever marketing strategies that in the end are not always good for patients. Originally, the *Orphan Drug Act* aimed at providing incentives for pharmaceutical companies to develop drugs for rare diseases. Nowadays, with orphan drugs becoming remarkably profitable [271], and with pharmaceutical companies dominating the market with their specific drugs, it might be imperative that the *Orphan Drug Act* be updated to prevent a monopolization of the market by large pharma.

2.2 The European Legislation

In Europe, the slow development of orphan drug legislation was not due to a lack of interest, but mainly because the EU had to be "created" with legislation, rules,

[270] *Supra* note 267 at 6.
[271] Thomson Reuters. 2012. "The Economic Power of Orphan Drugs." <http://thomsonreuters.com/products/ip-science/04_013/1001450.pdf>. (Accessed May 26, 2016).

agreements, and infrastructures established between all countries[272]. Now, the European Union is comprised of 28 European countries working in partnership economically and politically[273]. It is a unique association where these countries have partly renounced their sovereignty to EU institutions. Numerous decisions are thus made at the European level[274].

Historically, European Organization for Rare Diseases (EURORDIS), a federation of patient's associations which is active in improving the quality of life of patients affected with rare diseases, [275] played a major advocacy role for the implementation of the legislation.

The European Commission has estimated that 5,000 to 8,000 rare diseases exist in the EU and that 27 to 36 million people might be affected[276]. On December 16 1999, the European Parliament and the Council of the European Union passed a law on orphan medicinal products (same as the term orphan drug)[277]. This *Regulation*:

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[272] E Hernberg-Ståhl & M Reljanović, *Orphan drugs* (Woodhead Publishing Limited, 2013), doi: 10.1533/9781908818393.9, at 13.

[273] "European Neighbourhood Policy and Enlargement Negotiations - From 6 to 28 members - European Commission", online: <http://ec.europa.eu/enlargement/policy/from-6-to-28-members/index_en.htm>. (Accessed May 20 2016).

[274] "What is the European Union - EUintheUS.org", online: *Delegation of the European Union to the United States* <http://www.euintheus.org/who-we-are/what-is-the-european-union/>. (Accessed May 20-2016).

[275] "EURORDIS Rare Diseases Europe - Who we are?", online: <http://www.eurordis.org/who-we-are>. (Accessed May 26 2016).

[276] Zachary Brennan, "Orphan Medicines in the EU: A 15-Year Review | RAPS", online: <http://www.raps.org/Regulatory-Focus/News/2016/01/29/24205/Orphan-Medicines-in-the-EU-A-15-Year-Review/>. (Accessed May 25 2016).

[277] *European Commission (2000) Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999* (OJ L18/1, 22.2.2000). It is worth clarifying the term orphan medicinal product Article 2 defines: (b) 'orphan medicinal product' means a medicinal product designated as such under the terms and conditions of this Regulation; and Article 3 states the criteria for orphan medicinal product as: 1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate

> […] sought to protect the interests of RDs patient community by incentivising research and orphan drug development. Recognising that RD patients' basic needs were not being met, the EU adopted a rights-based approach for RD patients, underlining that they 'should be entitled to the same quality of treatment as other patients'. The Regulation aims to regulate and encourage innovation in the field of orphan diseases. It does so by establishing 'a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for research, development and placing on the market of designated orphan medicinal products' [278].

The European Union judiciously decided on a uniform approach for all countries when they passed the orphan medicinal product regulation. The EU wanted to benefit from the advantages of the broadest possible market while avoiding the dispersion of resources which are often scarce. Global contribution from countries also help in coordinating proactive actions directly aimed at the well-being of rare disease patients.

Therefore, following the signing of the *Regulation (EC) No 141/2000*, the community-wide regulations on orphan medicines came into force in April 2000 with the *Regulation (EC) No 141/2000* of the European Parliament and of the Council and the implementing Commission Regulation (EC) No 847/2000[279]. The purposes of the legislation provided " incentives for the research, development and marketing of orphan medicinal products that the pharmaceutical industry would be unwilling to develop

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sufficient return to justify the necessary investment;and (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

[278] Jasjote Grewal & Nils Hoppe, "Don't Forget the Orphans" (2015) 22:2 European Journal of Health Law 107 at 108.

[279] *Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and'clinical superiority* (OJ L 103/5, 28.4.2000) at 5.

under normal market conditions"[280]. The aims were quite similar to the *Orphan Drug Act*.

However, a key point in the legislation concerns the prevalence of individuals affected with rare diseases which was clearly defined by the EU (and is different from the US) as follows:

> […] a prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold; medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition should be eligible even when the prevalence is higher than five per 10 thousand[281];

A centralized Community procedure is used to introduce an orphan drug onto the market via article 7 of the *Regulation (EC) No 141/2000*[282]. The process for obtaining "orphan-medicinal-product designation" must respect a strict timetable which begins with a 3-month notification of intention to submit, followed by a 2-month pre-submission meeting where validation questions can be negated, and then the submission itself. The application (with specific forms and formatting required) goes through a scientific evaluation and review in a 90-day procedure. The application form requires details of the condition targeted, the proposed orphan drug indication, the medical plausibility, the justification of the life threatening nature of the condition, as well as the reference documentation, the information from databases, the prevalence and the incidence of the disease. It also requires the potential return on investment, the existence of other methods of diagnosis, prevention and treatment and as to why they are not

[280] Commission of the European Communities, Commission Staff working document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained Document on the basis of Article 10 of Regulation (EC) No 141/2000 Brussels, 20.6.2006 SEC(2006) 832.
[281] *Supra* note 277 s. 5.
[282] *Ibid* s. 7.

satisfactory. In addition, a justification of significant benefit, a description of the stage of development of the product and details of current regulatory and marketing history is also requested. All of this is accompanied by a complete scientific bibliography. The application is sent by individuals or companies to the European Medicines Agency (EMA, the Agency) via the Committee for Orphan Medicinal Products (COMP). This Committee is nominated by the European Commission. It is comprised of experts appointed by Member States, members on the EMA's recommendation, patients' organization representatives and non-voting COMP members[283]. The involvement of EURORDIS is also important at this stage of the application because "it facilitates the preparation of European Public Assessment Reports (EPARs) in the review process of marketing authorization applications of new medicines for rare diseases"[284]. In addition, EURORDIS takes part in reviewing public summaries of COMP opinion documents for orphan drug applications[285]. It terms of practical impact, this demonstrates the involvement of patients' organizations in the orphan drug process.

A single marketing authorization is granted and valid throughout the EU, offering the largest possible EU market. It is worth noting that this centralized process is now obligatory for orphan medicinal products since 2005[286].

[283] "European Medicines Agency - COMP - COMP members", online: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000005.jsp&mid=WC0b01ac0580028e76>. (Accessed May 25 2016).

[284] Chris Wilson, "Patient network and advocacy groups" in *Orphan Drugs* (Elsevier, 2013) 101 at 106. doi: 10.1533/9781908818393.101.

[285] *Ibid*.

[286] *European Commission Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency* (OJ L136/1, 30.4.2004)

2.2.1 Incentives Provided by the Regulation *(EC) No 141/2000*

Incentives for the development of drug treatments for rare diseases in the EU are similar to the ones in the US. Market exclusivity for the EU is 10 years, plus an additional 2 years of pediatric exclusivity for studies that qualify, whereas it is only 7 years in the US. The EU market exclusivity "prevents another application for a market authorization (MA) (and also the extension of an existing MA) for the same therapeutic indication, for a similar medicinal product"[287]. The market exclusivity is an important incentive but it comes into effect only when the MA is finalized in the EU. As in the US, there is an assistance for protocols and follow-up on the procedure, a reduced/waived regulatory fees, and a tax credit on clinical trials. However, the EU does not provide grant programs to subsidize research, which is a major difference from the US[288].

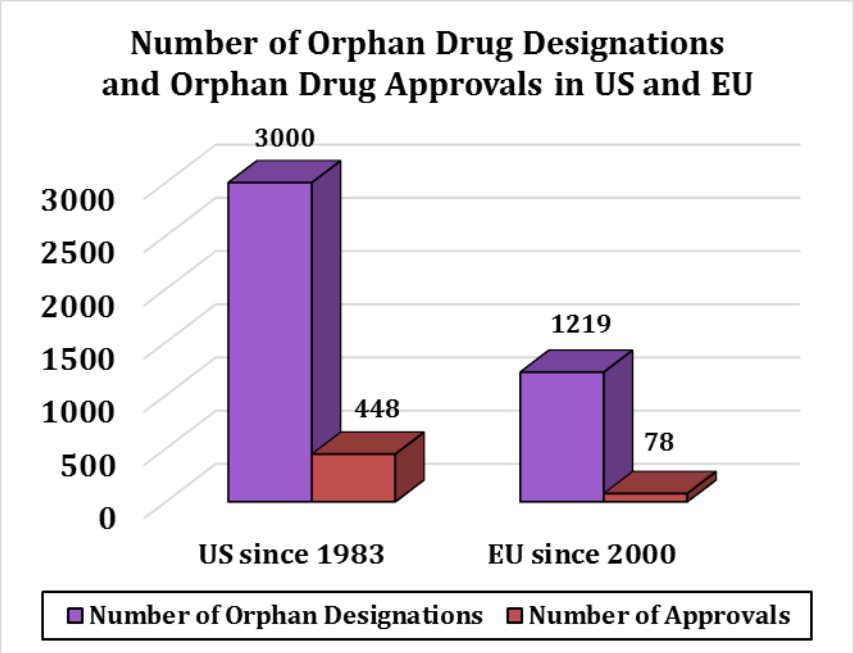
Five years after the implementation of the EU legislation (April 2000 to April 2005), there were 458 applications submitted to obtain an orphan designation. Of these, 268 products received a designation for over 200 different rare conditions. To clarify, submitting an application for an orphan drug designation provides a special status to a drug to treat a rare disease. Overall, the legislation for orphan drugs seems to be functioning well with the incentives provided. The number of applications has increased regularly from 2000 to 2004. In 2004, the number of approvals (75) was nearly 3 times the number of withdrawals (22).

A more recent report revealed that from 2000 to September 2015, the EMA has

[287] Anthony K Hall & Marilyn R Carlson, "The current status of orphan drug development in Europe and the US" (2014) 3:1 Intractable & Rare Diseases Research 1.at 1. doi: 10.5582/irdr.3.1
[288] *Supra* note 42.

received 2,302 applications for orphan designations, and of these the European Commission approved 1,544. Moreover, as of 2015, "1,227 orphan designations are active, as some decisions have expired and some products have been withdrawn by the sponsor"[289]. It might seem to be a high number of designations, but only 1% of rare diseases are covered by authorized drugs[290]. Data in Figure 9 aims to show a global major difference for the ratio of total designation/approval rate between US and EU. It shows that 14.9 % of orphan drug designations are approved in the US, whereas only 6.4% are approved in the EU.

Figure 9. Comparison between Total Orphan Drug Designations and Approval in the US and EU



Source: Our analysis from Hall and Carlson's data.

[289] *Supra* note 276.

[290] *Ibid*.

Again nothing is ideal in these complex processes and some aspects need to be improved. Negative comments about the long 6-month EU timeframe and the complexity of the process during the overall application procedure have been criticized[291].

2.2.2 The EU Reimbursement Procedure

The reimbursing procedure is also a major issue in the EU as it keeps patients from obtaining access to the orphan drug. Let us not forget that the last phases of the development and marketing of a drug is the patient gaining access to the orphan drug, receiving the drug as soon as possible after approval, and that the reimbursement of the cost be covered[292]. In EU, the reimbursement process differs according to members of the EU. In some cases "reimbursement is provided on approval, whereas in others, the procedures might take up to 4 years, while requiring the company to provide the product on a compassionate use basis in the meantime, due to the serious nature of the diseases to be treated"[293]. In some EU countries such as Sweden and Spain, the complexity of the process lies in the fact that the responsibility for providing healthcare has been transferred to regional authorities. Therefore, there might be disparities between patients to access the orphan drug even in different regions of the country, as in Canada, making it particularly complicated for them[294]. Another problem is that the Health Technology Assessment procedures are not well-adapted and they sometimes do not respect the

[291] *Supra* note 287 at 3-4.
[292] *Supra* note 262 at 248.
[293] *Ibid* at 249.
[294] *Ibid*.

"payer's criteria" for orphan drug reimbursement. This is mainly due to the high cost of the drugs, but also related to issues in showing benefits of the treatment (referred as clinical added value)[295].

Interestingly, the FDA and EMA have recently started working together to devise joint procedures for orphan drug designations. This has led to a uniform and common application form called "Common EMEA/FDA Application Form for Orphan Medicinal Product Designation" which is available for pharmaceutical companies (sponsors) applying for an orphan drug status in EU, as well as in the US. Moreover, upon common agreement, only one annual report may be submitted by sponsors for orphan drugs designated for both entities in order to simplify the process and eliminate the duplication of efforts[296].

Figure 10 shows comparisons between orphan drug designations and orphan drug approvals on a yearly basis in the US and EU since the inception of legislation in 1983 and 2000, respectively. Over the years, the increasing trend for orphan drug designations is similar for EU and US, whereas the orphan drug approvals is always higher in the US on a yearly basis (Figure 10).

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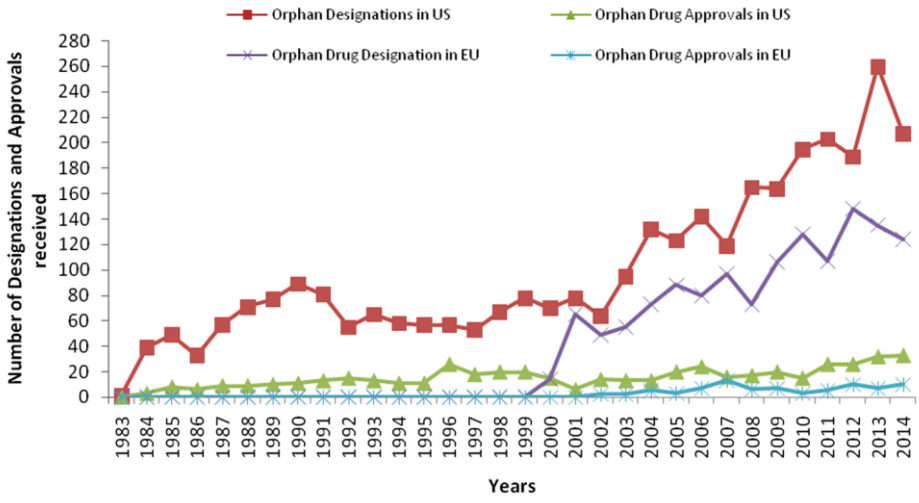
[295] *Ibid*.

[296] Jyoti Tiwari, "Navigating through orphan medicinal product regulations in EU and US--similarities and differences" (2015) 71:1 Regul Toxicol Pharmacol 63; The annual report "provides information on the status of the development of orphan medical products, including a review and status of ongoing clinical studies, a description of the investigation plan for the coming year, any anticipated or current problems in the process, difficulties in testing, and any potential changes that may impact the product's designation as an orphan product". "Press Announcements - International Collaboration: FDA and European Medicines Agency Agree to Accept a Single Orphan Drug Designation Annual Report", online: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm202300.htm>.(Accessed June 8 2016)

Figure 10. Yearly Comparison of Orphan Drug Designations and Orphan Drug Approval for EU and US



Source: J. Tiwari, Regulatory Toxicology and Pharmacology 2015

3. Orphan Drug Framework Proposal for Canada: A Possible Solution?

A Canadian study recently reported data on the changes happening in Canada regarding access to US-approved orphan drugs from 1997 to 2012. Their evaluation of data focused on regulatory and temporal access to orphan drugs. Their results have shown a paradigm shift in Health Canada's policies. In fact, in 1997, while 63% of US-approved orphan drugs received regulatory approval in Canada, the study reveals an increase to 74% from 1997 to 2012. "The majority of those drugs (150 of 206, or 73%) were approved for the same indication as the corresponding US orphan drugs"[297]. Moreover, their results revealed that the time to review an application in order to have access to an orphan drug is significantly longer in Canada (423 days) compared to the US (341 days). However, Canada does not have the same resources as the FDA to

[297] It should be mentionned that the US-approved orphan drugs that did not receive regulatory approval in Canada are not part of the 74%, but were, and always are, available through the Special Access Program. Matthew Herder & Timothy Krahn, "Some Numbers behind Canada's Decision to Adopt an Orphan Drug Policy: US Orphan Drug Approvals in Canada, 1997–2012" (2016) 11:4 Healthcare Policy | Politiques de Santé 70 at 75.

accelerate the process[298]. Nevertheless, there seems to be a change in Health Canada's policy and the regulatory approval of US-approved orphan drugs. Why has there been such a shift? We propose different reasons which might explain these changes.

First, the global growth of the orphan drug market has been regularly expanding (See Figure 4). Accordingly, the number of applications for the approval of orphan drugs for rare diseases has increased considerably over the last 20 years, creating a greater burden on the evaluation process. There is thus a willingness from Canadian authorities to rely more and more on the US, given the availability of their US-approved orphan drugs.

Moreover, we have earlier emphasized that in 2013, a total of 431 drugs were part of the SAP list in Canada. We also revealed a major discrepancy between the total number of SAP orphan drugs (n=127) in Canada and the ones already approved in the US (n=90) and Europe (n=62). We can assume that since there is legislation for orphan drug approvals in US and Europe, Health Canada has probably reoriented its policies over the years to facilitate regulatory approval of orphan drugs in Canada by relying again on the US-approved orphan drug procedure. Therefore this might explain the 11% increase of US-approved orphan drugs that received regulatory approval in Canada over the last 15 years.

Pressure from advocacy groups, such as CORD, is focused on the affordability and sustainability of access to orphan drugs[299]. CORD's approach mirrors the already

[298] *Ibid* at 78.
[299] Canadian Organization for Rare Disorders "CORD: Assuring Affordability and Sustainable of Access to Orphan Drugs" (2015) online : <http://new.raredisorders.ca//content/uploads/CORD-Assuring-Affordability-and-Sustainable-of-Access-to-Drugs-for-Rare-Diseases-copy.pdf> (Accessed April 20 2016).

existing legal framework in US and Europe and based on the fact that rare disease patients must "have access to the right drug in a timely fashion"[300].

The underlying problem lies in the cost of orphan drugs *versus* the small number of affected individuals with rare diseases. The debate would probably be less heated if the drug administered to patients was equivalent to the cost of an aspirin (about 0.05 cent/tablet).

3.1 Towards a Personalized Medicine Approach

The concept of personalized medicine is not new, since patients are usually treated individually, in their best interest by their physicians. But nowadays, what is new is the advancement of knowledge in the science and technology fields that has paved the way for genomics, proteomics, metabolomics, imaging technology, and novel pharmaceutical treatments. Suffice to say that orphan drugs are no exception when it comes to personalized medicine in the treatment of rare diseases.

In depth knowledge about the genome has revealed that for one specific disease there might be a marked heterogeneity in the phenotype as well as the genotype. This leads to the fact that two siblings in the same family, with the same parents having the same mutation might have different phenotypes, which will lead to different outcomes

[300] *Ibid*.

of the disease[301]. How can these novel improvements help in detecting patients, diagnosing them and treating them in the best way possible?

The FDA has described personalized medicine as follows:

> The term "personalized medicine" is often described as providing "the right patient with the right drug at the right dose at the right time." More broadly, "personalized medicine" may be thought of as the tailoring of medical treatment to the individual characteristics, needs and preferences of a patient during all stages of care, including prevention, diagnosis, treatment and follow-up[302].

Figure 11 shows a schematic diagram of the basic principles underlying personalized medicine[303]. The left side of the figure shows that in a "non-personalized" medicine approach, patients are all treated in the same way with a uniform dose of medication notwithstanding the specific clinical features of a patient. By contrast, a personalized medicine approach will specifically target the mutation of the patient and the correlations with disease severity and progression and hopefully offer the appropriate treatment according to the genotype. Since most rare diseases have a genetic component, the concept of personalized medicine becomes a significant asset for the Canadian healthcare system offering better medical strategies while using orphan drugs.

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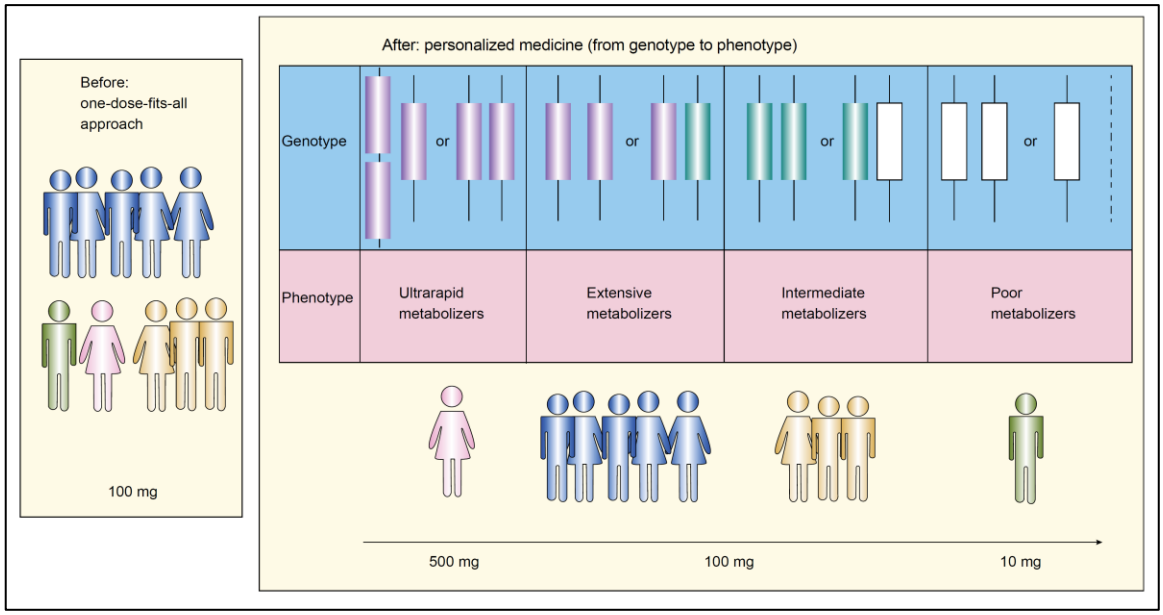
[301] M Rigoldi et al, "Intrafamilial phenotypic variability in four families with Anderson-Fabry disease: Intrafamilial phenotypic variability in Fabry disease" (2014) 86:3 Clinical Genetics 258. doi: 10.1111/cge.12261.

[302] U.S. Food and Drug Administration, "Paving the Way for Personalized Medicine, FDA's Role in a New Era of Medical Product Development", October 2013, online: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf > (Accessed April 15 2016).

[303] Hong-Guang Xie & Felix W Frueh, "Pharmacogenomics steps toward personalized medicine" (2005) 2:4 Personalized Medicine 325.

Figure 11. Schematic Diagram of the Basic Principles Underlying Personalized Medicine



Source: ***Personalized Medicine 2005***

This aforementioned figure illustrates the challenges found in treating patients affected with rare diseases and the selection of orphan drugs. As part of a personalized medicine focus, many questions come to mind: Who should receive the orphan drug? At what dose? At which frequency? If two orphan drugs are available on the market for the same disease, is one treatment better than the other? What are the criteria to access the drug? Should each province decide on the accessibility of the drug? Should the federal government be involved in deciding which orphan drug for a specific disease is reimbursed or not? Who can afford it? At what price?

3.2. Who Should Receive an Orphan Drug?

A core question when evaluating patients affected with rare diseases is who should receive the treatment with the orphan drug? This question is crucial because it involves an equity principle for patients affected with rare diseases in Canada to receive adequate treatment. This basic principle is part of the national (federal) health insurance program in place in Canada in conjunction with the provinces. It is often referred to "Medicare" and is:

> […] designed to ensure that all residents have reasonable access to medically necessary hospital and physician services, on a prepaid basis. Instead of having a single national plan, we have a national program that is composed of 13 interlocking provincial and territorial health insurance plans, all of which share certain common features and basic standards of coverage. Framed by the *Canada Health Act*, the principles governing our health care system are symbols of the underlying Canadian values of equity and solidarity[304].

Emphasis should be put on the words "equity and solidarity". These Canadian values are particularly relevant when it comes to funding orphan drugs. Article 3 of the *Canada Health Act* states that: "It is hereby declared that the primary objective of Canadian health care policy is to protect, promote and restore the physical and mental well-being of residents of Canada and to facilitate reasonable access to health services without financial or other barriers"[305]. According to this legislation, patients affected with rare

[304] *Supra* note 160; See also Health Canada Government of Canada, "Canada's Health Care System (Medicare) - Health Canada", (16 May 2005), online: <http://www.hc-sc.gc.ca/hcs-sss/medi-assur/index-eng.php>. (Accessed May 2 2016).
[305] *Supra* note 160.

diseases needing orphan drugs should also have their fair share of the health budget and a right to effective and high-quality care. It was stated that there should be a "basic moral and public policy commitment to non-abandonment of individuals with needs for highly specialized health care when making policies for rationing and resource reallocation, even in resource constrained settings"[306].

The second aspect to be considered while evaluating who should receive an orphan drug concerns the medical evaluation of the patient. This is an important phase to determine if a patient should receive the drug or not. In principle, these aspects should be addressed notwithstanding the cost of the drug.

We thus believe that there should be well-established criteria or guidelines to decide who should receive an orphan drug for a specific rare disease. These guidelines should be implemented in a uniform way and be applicable to all provinces in Canada for each specific disease, without discrimination due to age and gender.

We would like to describe a step-by-step procedure to ensure robust guidelines on who should receive orphan drugs for rare diseases. The process to establish these guidelines should start with a pan-Canadian (national) scientific committee having the expertise in the rare disease at stake with the goal to define evidence-based specific guidelines for the targeted disease. The members of the committee should have experience in treating patients and have expert knowledge on all aspects of the disease. This committee comprised of physicians and specialists treating these patients, as well as

[306] C A Gericke, "Ethical issues in funding orphan drug research and development" (2005) 31:3 Journal of Medical Ethics 164. doi: 10.1136/jme.2003.007138

scientists, would first review the literature in order to gather the most recent information on:

- the clinical and scientific aspects of the disease;

- the natural history of the disease;

- the age at onset of symptoms;

- the impact and outcomes of treatment;

- the adverse events encountered related to treatment;

- the risk factors for patients receiving treatment;

- the contraindications and/or cessation of the treatment;

- the potential benefits of the treatment;

- the biomarkers to evaluate the efficacy of treatment[307];

- the comparison of dosage for the treatment, if applicable.

The guidelines should be determined in an unbiased manner, and without possible or foreseeable conflicts of interest on the part of members of the scientific committee. These guidelines should always be reviewed each year in order to offer the highest standard of care for patients taking into account the advancement of technologies and the growing medical and scientific knowledge of the disease.

An example of this process has already been implemented in Canada, for only one rare disease, Fabry disease, a multisystemic lysosomal storage disorder. As mentioned

[307] Christiane Auray-Blais et al, "Urinary biomarker investigation in children with Fabry disease using tandem mass spectrometry" (2015) 438 Clin Chim Acta 195.

previously in section 1.2.2, CFDI was devised in 2006[308], as part of a clinical trial in Canada. Before that, in 2005, an expert committee proposed recommendations for diagnosis, management and enzyme replacement therapy in Canada as part of a first draft for Canadian Fabry guidelines[309]. The committee then stipulated that:

> The establishment of Canadian guidelines for the diagnosis and management of Fabry disease will serve as an initial model for the establishment of a national process for guideline development for other lysosomal storage diseases as well as other rare genetic diseases. Further outcome studies in patients who have had therapy commenced early in their disease will be needed to refine these guidelines. Although it is hoped that early initiation of therapy i.e. prior to significant disease manifestations or complications, may result in improved outcomes for patients, this has yet to be systematically studied. In addition, further studies are necessary to establish the optimum dose of recombinant enzyme that will lead to prevention of storage or reversal of specific disease manifestations. The role of enzyme replacement therapy for Fabry disease in childhood also requires systematic investigation. For all of these reasons, we urge that Canadian patients with Fabry disease be entered into a confidential registry that will capture demographic and treatment status to direct future research and refinement of treatment.

The ongoing CFDI study has a control group which is essential to compile natural history data to allow the evaluation of the effects of therapy treatment. The CFDI also has a registry that is independent of pharmaceutical companies involved in the treatment of Fabry patients and of government influence[310]. The registry is comprised of various demographic data such as age, gender, and clinical data related to manifestations of the

[308] S Sirrs et al, "Baseline characteristics of patients enrolled in the Canadian Fabry Disease Initiative" (2010) 99:4 Molecular Genetics and Metabolism 367. doi: 10.1016/j.ymgme.2009.11.001.
[309] Lorne A. Clarke et al, "Fabry Disease: Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy in Canada",(2005), Canadian Fabry Guidelines: draft.
[310] *Supra* note 308.

disease (renal, cardiac, cerebrovascular diseases). A registry containing reliable data becomes an incredible tool to evaluate the efficacy of treatment, and the overall follow-up of patients, as well as to ameliorate the care of patients, and eventually the healthcare system. Considering the low number of affected rare disease patients, it will also help achieve larger cohorts for clinical research. It was stated that "confounding the paucity of available research, many rare diseases are often classified within broader diagnostic categories, which results in difficulties creating reliable data registries"[311].

In our opinion, well-defined guidelines for each rare disease would definitely address the question of who should receive the drug. Longitudinal clinical trials involving patients affected with rare diseases would also address major issues such as the ideal dose provided to patients, as well as the optimal dose frequency, this being part of a personalized medicine approach.

Another key question: if two competitive orphan drugs are available on the market for the same disease, is one treatment better than the other? A multicenter clinical trial involving the highest number of affected patients, would allow better statistical power analysis and responses to this query.

We therefore recommend the implementation of a committee who would devise guidelines for each rare disease to determine who should receive an orphan drug. These guidelines should first be devised through clinical trials, and then would be implemented as novel healthcare policies for the regular practice of physicians.

[311] Fishman Jesse C & Skrepnek Grant H, "Pharmacoeconomic analyses of treatments for rare disease" (2012) 1 Pharmaceuticals, Policy and Law 51. doi:10.3233/PPL-2011-0336.

3.3. Should Each Province Decide on the Access to Orphan Drugs?

The major hurdle to gain access to orphan drugs is the cost of the drug and its reimbursement. In fact, governmental authorities are reluctant to provide reimbursement for expensive orphan drugs for life-long treatment, even if they are for a small number of patients.

As described previously in section 1.2, different procedures/strategies have been instigated in each province in Canada for patients affected with rare diseases to access orphan drugs. Above all, these processes are cumbersome and time-consuming. This was confirmed by the study of Menon and colleagues who compared the mechanisms in place throughout Canada for orphan drug reimbursement and evaluated the impact on the access to these drugs[312]. The study shows that there are formal and informal processes to access orphan drugs and that some provinces have dedicated programs for orphan drugs, but in the end, there is no agreement on access between provinces/territories. This leads to problems of access to orphan drugs at various levels. Patients who move from one province to the other might have to start the whole access procedure from the beginning, and might subsequently have the province deny the application because the drug is not reimbursed in this particular province. Patients might have to cease the treatment of life threatening diseases for an undefined period that might cause clinical manifestations, which would not otherwise have happened. The

[312] *Supra* note 167.

follow-up of these patients might be difficult to assess by physicians, if patients frequently interrupt treatment.

It was correctly stated that "the availability of and access to orphan drugs play a key role in determining whether patients will receive adequate and efficient treatment"[313]. This latter study comprised of 11 countries, which are Australia, Canada, England, France, Germany, Hungary, the Netherlands, Poland, Slovakia, Switzerland and the US, was devised to examine their pharmaceutical markets for four rare diseases (pulmonary arterial hypertension, Fabry disease, hereditary angioedema and chronic myeloid leukaemia). Briefly, results revealed that:

> Although the present study showed some variations between countries in selected indicators of availability and access to orphan drugs, virtually all of the drugs in question were available and accessible in our sample. However, substantial co-payments in the US and Canada represent important barriers to patient access, especially in the case of expensive treatments such as those analysed in this study[314].

The co-payment plan in Canada varies according to provinces. It can involve various private and public payers for medications and extensive direct costs to patients "by way of deductibles, co-payments or co-insurances"[315].

In conclusion, provinces should have a uniform procedure to decide who should have access to orphan drugs, as part of a global Canadian model in an alliance with the federal government. Working together to establish a formal agreement between

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[313] Carl Rudolf Blankart, Tom Stargardt & Jonas Schreyögg, "Availability of and access to orphan drugs: an international comparison of pharmaceutical treatments for pulmonary arterial hypertension, Fabry disease, hereditary angioedema and chronic myeloid leukaemia" (2011) 29:1 Pharmacoeconomics 63.
[314] *Ibid*.
[315] *Supra* note 156 at 19.

provinces and financial support from the federal government would be beneficial because it would regroup resources which are often limited and target a wider orphan drug market. It will also avoid time-consuming uncoordinated measures for the healthcare system and patients.

3.4 The Pharmacoeconomic Aspects for Orphan Drugs

The subject of very expensive orphan drugs for patients with rare diseases related to pharmacoeconomics has been discussed for a number of years. In a society where resources are scarce, it becomes imperative to "identify, measure and compare the cost and consequences of drug therapy to healthcare systems and society"[316]. The cost and reimbursement of orphan drugs for life-threatening diseases remain problematic and should be prioritized for patients, politicians, legislators, pharmaceutical industry leaders, health care professionals (general practitioners, medical specialists, administrative officers, etc.), and academic researchers.

3.4.1 CADTH: a Possible Paradigm Shift?

Discussion about access to orphan drugs and reimbursement have been recurring in Canada since there is no official orphan drug policy. A good example of this refers to March 2016 where the CADTH published a new recommendation framework putting the emphasis on clinical considerations, unmet need and "real-world evidence":

> In exceptional cases where there is uncertain clinical and pharmacoeconomic evidence, the CADTH drug expert

[316] Lisa Sanchez Trask, "Chapter 1. Pharmacoeconomics: Principles, Methods, and Applications" in Joseph T DiPiro et al, eds, *Pharmacotherapy: A Pathophysiologic Approach, 8e* (New York, NY: The McGraw-Hill Companies, 2011).

> committees may issue a recommendation to reimburse with clinical criteria and/or conditions, due to practical challenges in conducting robust clinical trials and pharmacoeconomic evaluations and in the presence of significant unmet medical need. In these situations, although there is uncertainty with the clinical evidence, the available evidence must reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease. Significant unmet clinical need is identified on a population or subpopulation basis (i.e., not on an individual basis) through the CDR and pCODR processes[317].

This possible CADTH paradigm shift might be due to the low recommendation rate for reimbursement of orphan drugs in Canada compared to other countries for the same drugs. Also, discrepancies from five Canadian jurisdictions were found on health technology assessment (HTA) showing a lack of concordance:

> It should also be noted that there was a considerable lack of concordance in HTA decisions between the different agencies. For the drugs reviewed by all five jurisdictions, there was only a 33.3% concordance in decisions, suggesting a lack of standardization in the methods used to assess the strengths and weaknesses of the limited clinical and economic data available for orphan drugs. This was particularly apparent in orphan drug reimbursement concordance between CDR and Quebec. In this case concordance was only 68%, reflecting variable interpretation of common efficacy data in a health care system with presumably similar cost constraint [318] .

[317] CADTH. "Recommendation framework for CADTH Common Drug Review and pan-Canadian Oncology Drug Review Programs: Guidance for CADTH's Drug Expert Committees" Par. 2.1.2, March 2016.online: <https://www.cadth.ca/media/cdr/templates/pre-sub-phase/CDR_pCODR_ recommendations_framework.pdf.> (Accessed March 29, 2016); McKesson Canada "Towards a New Way of Evaluating Orphan Drugs at CADTH", 2016, online: <http://www.canadianinstitute.com/content/download-content/marketing-materials/350X16/Orphan-Drugs-at-CADTH_McKesson.pdf> (Accessed May 28 2016).
[318] *Ibid*.

Additionally, after CDR submissions in Canada, the positive recommendation rate for a same drug compared to other countries revealed major discrepancies: in Australia (88.1%), in Scotland (60%), in New Zealand (62%), and in Québec (66%), where for the latter, the HTA system is independent from CDR because of INESSS[319].

We find these statistics particularly troubling. At the present time, it seems that Canadian patients are not receiving reimbursement for some orphan drugs for rare diseases which are accepted elsewhere. Therefore, there is a lack of concordance for the evaluation of reimbursement. This definitely leads to inequities among Canadian citizens affected with rare diseases compared to other countries.

3.4.2 Cost-Effectiveness Analysis for Orphan Drugs: Is It the Best Solution?

Efforts concerning orphan drug economic evaluations aimed at guiding decisions for drug reimbursement, including the cost, have been hampered by specific features that are inherent to rare diseases. It has been rightly stated that:

> The economic evaluation of orphan drugs is inhibited by the existence of often limited and weak clinical data at launch time. In the context of rare diseases, it may prove difficult to recruit a sufficient number of patients and medical centers in clinical trials, thus raising costs. Orphan drug trials (in for example the field of oncology) may be halted early on ethical grounds when an interim analysis demonstrates clinical superiority of the orphan drug in terms of an intermediate outcome measure such as progression-free survival. It has been recommended to allow greater use of surrogate outcome measures for orphan drugs if clinical data are incomplete, but impose at the same time a commitment to continue research[320].

[319] *Ibid*. Unfortunately, these data referred to a manuscript in preparation (2016).
[320] Steven Simoens, "Pricing and reimbursement of orphan drugs: the need for more transparency" (2011) 6:1 Orphanet Journal of Rare Diseases 42.

Nevertheless, different conventional techniques have been used to determine the cost effectiveness of orphan drugs. One technique particularly used by healthcare administrators/decision makers is the cost-effectiveness analysis (CEA). This technique provides "policy comprehensive information regarding treatment alternatives concerning differences in resource consumption and cost as a function of economic, clinical, or humanistic outcomes"[321]. Within the CEA, a statistical tool used is the incremental cost-effectiveness ratio (ICER) that involves the comparison of new technologies. Such technologies include novel treatment, novel orphan drugs, clinical interventions, other new diagnostic procedures to current treatment, and other standards of care. In other words, ICER takes into account the opportunity cost associated with using numerous therapeutic alternatives. Different pharmacoeconomic tools can be used separately, or in combination when evaluating cost effectiveness of an orphan drug:

> Although clinical outcomes such as mortality (e.g., life-year gained, LYG) often constitute the basis of CEA, extensions beyond this methodology utilizes the quality-adjusted life-year (QALY) in a framework designated a cost-utility analysis (CUA); the CUA incorporates both the length of life with the quality of that life. Additionally, a cost-benefit analysis (CBA) monetizes a change in health effect associated with a new intervention to yield a relative cost per treatment intervention versus alternatives[322].

Nonetheless, these aforementioned tools are not ideal for determining the cost effectiveness of orphan drugs for rare diseases. In fact, threshold values for these tools might be misrepresenting the cost effectiveness evaluation, as they do not take into considerations such as the availability of financial resources, the access to treatment, the

[321] *Supra* note 311.
[322] *Ibid*.

efficacy of treatment, the will to pay, and budget justifications/restrictions [323] . Additionally, the equity-weighing factor "to allow all persons the ability to live a normal life span" should be taken into account for QALY, since it is an important criterion. As "for patients with rare diseases, assigning a weighted QALY may better reflect society's willingness to make equity-based adjustments in certain circumstances for the distribution of health care resources"[324].

Another strong critique on the cost-effectiveness of treatment for rare diseases indicates that "it is virtually impossible to assess cost-effectiveness of treatments for rare diseases using conventional criteria"[325]. Why is it this way? Well, mainly because of the rarity of these diseases. In fact, due to the small number of patients affected with rare diseases, it is difficult to achieve statistical power analysis to establish the benefits of an orphan drug therapy. In addition, these rare diseases show a marked variability in the genotype and phenotype affecting multiple systems with variable clinical outcomes in patients. Hence, it becomes difficult to show a distinct effect of the therapy on the mortality rate or morbidity. "In many patients, the most common causes of morbidity are inherently difficult to quantify. This is true, for example, of Fabry disease, a lysosomal disorder in which irregular episodes of severe pain are one of the most consistent causes of morbidity[326]".

In our opinion, these cost-effectiveness evaluation tools of orphan drug for rare diseases are clearly not adapted to help governmental authorities and healthcare

[323] *Ibid*.
[324] *Ibid*.
[325] Joe T R Clarke, "Is the current approach to reviewing new drugs condemning the victims of rare diseases to death? A call for a national orphan drug review policy" (2006) 174:2 CMAJ 189.
[326] *Ibid*.

professionals in Canada to decide on the funding of drugs, and the subsequent reimbursement process. We strongly believe that a comprehensive framework for cost-effectiveness adapted specifically for rare diseases is necessary to better reflect the overall picture regarding the funding of orphan drug to ensure fairness, consistency and transparency for rare disease patients.

3.4.3 Framework for Guidance for Public Orphan Drug-Funding

Taking in mind the inconsistencies in the positive recommendation rates for orphan drugs throughout Canada and other countries, as well as issues with the cost-effectiveness, a questions arises: would a framework to evaluate orphan drug for rare diseases be a solution for public funding of these drugs in Canada? In our opinion, considering the lack of guidance for public orphan drug-funding for rare diseases in Canada, such a framework becomes a possible solution.

In fact, a model framework was devised in 2012 at the request of the Ontario Ministry of Health and Long-term Care, the objective being to offer "guidance for public drug-funding policy from the payer perspective"[327]. This evaluation was deemed necessary because of the limitation in obtaining information with randomized clinical trials on the effectiveness of a novel orphan drug for rare diseases. Unfortunately, the scientific literature does not provide guidance in this rare diseases context. The authors recognized that "The Canadian provinces and territories have attempted to develop a national strategy, but in the absence of a funding commitment from the federal government, this work has stopped, and so provincial funding recommendations

[327] Eric Winquist et al, "An evaluation framework for funding drugs for rare diseases" (2012) 15:6 Value Health 982.

considering efficacy and value for money in a conventional manner are typically negative[328]. Therefore, a committee called Drugs for Rare Diseases Working Group was created for this study and comprised of nine experts: three members from the Ontario Ministry of Health and Long-term Care (the Executive Officer and two pharmacists), two physicians, a pharmacist, a health economist, a pharmacoeconomist, a pediatrician-geneticist treating children affected with inborn errors of metabolism in children, and an ad-hoc ethicist. There were seven steps to the framework:

> Step 1: confirm that the disease to be treated with an orphan drug is really rare;
>
> Step 2: understand the pathophysiology, natural history, and health problems of the disease;
>
> Step 3: understand the probable value of the orphan drug;
>
> Step 4: evaluate the possible clinical effectiveness of the orphan drug;
>
> Step 5: evaluate cost consequences and prepare a funding recommendation;
>
> Step 6: validate the orphan drug model by having it reviewed by other disease experts and stakeholders;
>
> Step 7: continuously review and add novel information on the natural history of the disease, the cost or effectiveness of the orphan drug therapy and its impact[329].

This evaluative model was applied to Hunter's disease (MPS Type II) for the assessment of idursulfase, an orphan drug provided by infusion to the patients. Hunter's disease is a lysosomal storage disorder leading to either a severe, progressive

[328] *Ibid* at 982.
[329] *Ibid* at 983-985.

neurological and respiratory form of the disease (MPS type IIA) or an attenuated form of the disease with musculoskeletal abnormalities but without cognitive involvement (MPS type IIB). The framework evaluation led to the conclusion that patients affected with MPS type IIB receiving the orphan drug idursulfase therapy would have reduced progression of the disease by 10%, 20% and 50% and might have a longer life expectancy of 1.32, 2.93 and 10.66 years, whereas the life expectancy would have been only 0.03, 0.06, 0.16 considering that the drug does not reduce the progression of the disease for an 11-year old MPS type IIA patient having the more severe form of the disease[330].

The cost of idursulfase is estimated at $375,000 CAD per patient. Even if a detailed cost analysis was not possible, the framework evaluation study led to a concrete public funding decision of the orphan drug by the Ontario Minister:

> Detailed cost analysis was not done because the drug was not considered cost-effective by conventional criteria even in the most extreme model scenarios. However, the potential life expectancy gains in type B patients were considered highly valued. This was reviewed and approved by the Executive Officer, and a funding algorithm was developed for negotiation with the manufacturer (step 5). A review of the Markov model by content expert physicians was conducted. This led to revision of some assumptions and general approval of the process and its results. The framework was also presented to and approved by the Ontario Public Drug Programs Citizens' Council (step 6). Negotiations with the manufacturer led to the public funding of idursulfase in Ontario for patients 6 years or older without neurocognitive symptoms, while the manufacturer manages requests for funding for patients younger than 6 years of age in whom the potential effects on life expectancy were far less certain. This has provided an estimate of the annual cost of idursulfase to Ontario Public

[330] *Ibid* at 985.

> Drug Programs prioritized to those patients most likely to benefit. No new information informing the model has been identified to date (step 7).

In conclusion, this framework revealed that even in the context of dealing with a rare disease, where the patient may have various clinical outcomes (severe and attenuated forms of the disease), treated by a very expensive drug, with no adequate randomized clinical trials, it is possible to address public funding issues which lead to fair and transparent decisions in the aforementioned Ontario study. In the situation involved, the framework tried "to identify an evidence-derived "middle-ground" that is an improvement over arbitrary decisions based on either the absence of specific data or political expediency"[331].

In our opinion, guidance frameworks for public orphan drug-funding reimbursement should be established for rare diseases across Canada directed by an expert pan-Canadian (national) committee who would have the expertise in each rare disease evaluated.

3.4.4 Financial Repayments for Profitable Orphan Drug Designations

Highly US profitable orphan drug designations defined as those with an annual global sales of more than one billion $US (blockbuster drugs) are numerous. From data up to 2009, 43 orphan drugs were part of that group. From these, 18 were approved uniquely as orphan drugs and reached the one billion sales status within the 7-year

[331] *Ibid*.

exclusivity market period allowed for orphan drugs[332]. Some of these drugs have five or more orphan drug designations each (e.g. Novoseven, Neupogen, Gleevec, Remicade)[333]. Using the analysis of corporate reports, it was shown that 33 orphan designated drugs have record sales of $100 to $999 million US, where 19 are approved as orphan drugs exclusively in the US. It shows that the orphan drug market is more and more profitable, even with a low number of affected patients. Besides, some drugs having the same molecular active chemicals (e.g. interferon, somatropin and levocarnitin) can receive as many as 33 orphan designations per orphan drug with the intention to offer treatment to larger populations, which might be in violation of the prevalence defined by the ODA of fewer than 200,000 individuals[334]. Therefore, these blockbuster drugs become quite profitable probably due to all these various designation possibilities[335].

In the event of an orphan drug regulatory framework in Canada, it would be important to control the high cost of orphan drugs by price control-measures and repayments from companies who largely benefit from these lucrative orphan drug revenues. One of these might be a compensation sales tax on orphan drugs for companies having blockbuster drugs within 8 years of the market exclusivity, as well as those having high revenues that could be determined by the Board. This would be in accordance with the Japanese situation where it is an obligation for pharmaceutical companies to pay a "1% sales tax on orphan drugs with annual profits exceeding 100

[332] Olivier Wellman-Labadie & Youwen Zhou, "The US Orphan Drug Act: rare disease research stimulator or commercial opportunity?" (2010) 95:2-3 Health Policy 216.
[333] *Ibid*.
[334] *Ibid*.
[335] *Ibid*.

million yen (or $1,200,000 CAD) until government subsidies received by manufacturers have been repaid"[336].

In Canada, this repayment process could be managed by the Board and would allow support for the process evaluation of orphan drugs, as well as provide funding grants for R&D on orphan drugs.

Another important measure would be to control the prices for orphan drugs. Considering the global growth of the orphan drug market and the impact of high price drugs on the access for rare disease patients, there is a strong need to have an international consensus on the control of these prices. Countries around the world, under the tutelage of an international committee on orphan drug, could be responsible to adopt policies to regulate prices. This approach would bring a robust negotiable power because of country regrouping and offer the same price for orphan drugs to patients affected with rare diseases wherever they are.

3.5 Recommendations and Measures for Implementation of a Policy Framework for Orphan Drugs

As previously mentioned, in 2012, a regulatory framework for orphan drugs in Canada was released as an initial draft discussion[337]. Although there has yet to be an implemented framework for orphan drugs, it is critical to address certain points for future recommendations.

[336] *Ibid*.
[337] *Supra* note 158.

The definition of the term rare disease is an important one as mentioned previously, since it is used for the definition of an "orphan drug". It also represents a criterion to allow sponsors to apply for an orphan drug designation. According to the Canadian draft submitted on December 13 2012:

> Definitions would include a definition of the term "orphan drug" to mean a drug that meets the following criteria:
> a. The drug is intended for the diagnosis, treatment, mitigation or prevention of a life-threatening, seriously debilitating, or serious and chronic disease or condition affecting not more than five in 10 thousand persons in Canada; and
> b. The drug is not currently authorized by the Minister or if currently authorized, it will provide a potentially substantial benefit for the patient distinguishable from the existing therapy.

It seems that the broad definition of a rare disease is following the steps of the European legislation. The reason for this limit of fewer than 5 cases per 10,000 inhabitants in Europe originally, was to have a threshold value just below the cost-benefit for a pharmaceutical company of new drugs that were not profitable[338]. That being said, would the same measure be a good fit for Canada? Especially knowing that "most prevalence figures currently available in the literature refer to the so-called prevalence at birth, a term that is not always uniformly applied"[339]. The rare disease status according to the prevalence of the disease varies from country to country. It is really up to governmental authorities to determine the cut-off value for the prevalence. Furthermore, criteria under the orphan drug definition have to be met in order to qualify for an orphan drug designation. This might lead to major shortcomings, because the definition is

[338] *Supra* note 45 at 21.
[339] *Ibid*.

clearly not universal. In fact, the US prevalence is fewer than 200,000 meaning 0.075 per cent of the total population whereas the European Union used 0.05 per cent of the total population[340].

In our opinion, and similar to others[341], before implementing new legislation for orphan drugs, one option is to increase the control of the Patented Medicines Review Board to the extent of the SAP. We have previously stated that the mechanisms used by the Board have been inadequate in terms of prices since it is limited to patented drugs and even then, it has limited power to act or control exorbitant prices. Consequently, the Board should serve as a "guardian" for patented orphan drugs, but also for old off-patent drugs whose prices have increased due to financial reasons. That said, if a legislation is proposed in the future, it is worth taking into consideration that orphan drug programs could lead to new patents (even on old substances) and therefore would bring them back under the supervision of the Board –creating a certain control over prices.

However, there is still a possibility of commercial and ethical abuses when a new drug off the market is reinstated as an orphan drug. In fact, the situation of a pharmaceutical drug previously on the market that was eventually discontinued, then it received an orphan drug designation (either on the same trade name or not) has occurred numerous times in the US[342]. For example, Baclofen a drug who was approved in 1977, later discontinued, and then obtained an orphan drug designation in 1987 and 1991 with

[340] Bao-cheng Liu et al, "A cross-national comparative study of orphan drug policies in the United States, the European Union, and Japan: towards a made-in-China orphan drug policy" (2010) 31:4 J Public Health Policy 407.
[341] Garret Kent Fellows & Aidan Hollis, "Funding innovation for treatment for rare diseases: adopting a cost-based yardstick approach" (2013) 8 Orphanet J Rare Dis 180; Eve A Roberts, Matthew Herder & Aidan Hollis, "Fair pricing of 'old' orphan drugs: considerations for Canada's orphan drug policy" (2015) 187:6 CMAJ 422.
[342] Discontinued Pharmaceutical drugs that obtained a new life as orphan drugs are: aminosidine, Gabbromicina, Paromomycin, cromolyn and Gastrocrom which are part of 26 others. *Supra* note 332.

a final approval for orphan drug in 1992[343]. In addition, as mentioned previously, the ODA incentives have led to the salami slicing effect, a situation that should be not taken lightly by Canadians authorities.

On the other hand, what about the risk of getting an orphan drug patent for an existing off-label use, thereby potentially increasing price and decreasing access? In our opinion, different recommendations should be implemented in Canada as part of a policy framework to remove barriers to access orphan drugs for rare diseases. These recommendations would target all provinces and offer a uniform process that would benefit all Canadian citizens affected with rare diseases. These recommendations could be part of a Canadian policy framework.

Recommendation 1. Governmental funding for academic research should be increased in Canada to gain knowledge on the natural history and pathophysiology of rare diseases, as well as for orphan drug development.

Recommendation 2. A personalized medicine approach should be implemented to improve all stages of care for patients affected with rare diseases, including detection, diagnosis, treatment with orphan drugs and follow-up.

Recommendation 3. Due to the infrequency of rare diseases, a registry containing reliable data should be implemented in Canada for each rare disease, to assess the prevalence of the disease, the efficacy of treatment, the overall follow-up of patients, as well as to achieve larger cohorts for clinical research studies.

[343] *Ibid*.

Recommendation 4. A pan-Canadian (national) scientific committee should be implemented for each specific rare disease to establish evidence-based guidelines for patients to access orphan drugs uniformly in all provinces. These guidelines (accessible online) should be reviewed regularly to offer the highest standard of care for patients.

Recommendation 5. A formal agreement with a centralized procedure, between provinces and the federal government providing financial support, should be established for public orphan drug funding reimbursement for each rare disease, under the direction of an expert pan-Canadian (national) committee.

Recommendation 6. The Patented Medicines Review Board in Canada should serve as a "guardian" for prices of patented orphan drugs, but also for old off-patent drugs. The Board should extend its control over the Special Access Programme.

Recommendation 7. The Board should determine a compensation sales tax on orphan drugs for companies having blockbuster drug revenues within 8 years of the market exclusivity.

Recommendation 8. A worldwide consensus to control orphan drug prices should be established under the tutelage of an international committee responsible for adopting a policy framework to regulate prices.

Conclusion

The societal challenges and political debate surrounding orphan drug for patients affected with rare diseases has been going on incessantly in Canada. Many countries

have implemented orphan drug legislation, but Canada is still lagging behind. However, is there a need for a pan-Canadian (national) orphan drug framework?

In order to respond to this question, we need to understand that multiple factors reflect the complexity of these rare diseases, which affect a small number of patients. In fact, there is still no consensus for countries to arrive at a specific prevalence indicating the rarity of these diseases. There is also a lack of information on the natural history and pathophysiology of many rare diseases. Marked heterogeneity in the phenotype and genotype of most rare diseases increases the complexity of monitoring, management and follow-up of affected patients. This contributes to difficulties in designing robust clinical trials to assess safety and efficacy of orphan drugs with a statistical power analysis.

The purpose of this thesis was to evaluate some of the difficulties regarding the legal and policy framework, considering the fact that there is no orphan drug legislation in Canada, but also to evaluate how to reduce barriers and improve access to orphan drugs for rare diseases.

Considering that in Canada, the administration and delivery of health care services is under the responsibility of each province, our analysis showed that the application process for patients to access orphan drugs is time-consuming and labour-intensive. There are also major discrepancies between provinces to reimburse orphan drugs. Some drugs are accepted on a case-by-case basis by provinces according to their own conditions. A concrete example of differences between provincial coverage regard the orphan drug (Myozyme) for Pompe disease patients, which is reimbursed in Manitoba but not covered in British Columbia. Moreover, a study revealed that the recommendation rate for orphan drugs in Canada was lower than other countries for the

same drugs and that the health technology assessment varied within Canada. We found these statistics particularly troubling because it seems that Canadian patients are not receiving reimbursement for some orphan drugs for rare diseases which are accepted elsewhere. The lack of concordance for the evaluation of reimbursement leads to inequities for Canadian patients affected with rare diseases compared to other countries.

The evaluation of the US and the EU orphan drug legislation helped to understand the intricacies of policy mechanisms. It also provided incentives to pharmaceutical companies involved in the development and marketing of orphan drugs and also led to comprehend limitations of such legislation.

Advocacy groups are lobbying for orphan drug legislation in Canada via CORD, but even if there is an eventual legal framework in Canada for orphan drugs, there still might be recurrent problems in terms of reimbursement decisions. A reason for this is that provinces are responsible for their own delivery of health care services. Creating a centralized procedure to authorize orphan drugs similar to the US and European models will not fix everything. Having a legal framework with incentives for developing drugs might however increase R&D funds for orphan drug development. Nonetheless, the decentralised procedure for drug pricing and decision-making for reimbursement might still be a burden for patients between provinces to have access to these drugs. In terms of orphan drugs for rare diseases and the Canadian health policy-makers involved, it is crucial to differentiate between market approval and market access. One does not lead to the other, and unfortunately, Canada is way behind on both compared to other countries.

In our opinion, before implementing a legal framework, we need to address current problems. Therefore, we propose explicit recommendations in a policy

framework that will remove some barriers and improve access to orphan drugs; increase governmental funding for academic research; implement a personalized medicine approach for patients affected with rare diseases, including detection, diagnosis, treatment with orphan drugs and follow-up; implement a registry containing reliable data for each rare disease; implement a pan-Canadian (national) scientific committee for each specific rare disease to establish evidence-based guidelines for patients to access orphan drugs uniformly in all provinces; establish a formal national agreement by an expert pan-Canadian (national) committee for public orphan drug funding for each rare disease; increase the role and control of the Patented Medicines Review Board in Canada for prices of patented orphan drugs and also for old off-patent drugs; establish a compensation sales tax on orphan drugs for companies having blockbuster drug revenues; and establish a worldwide consensus to regulate orphan drug prices with an international committee adopting a policy framework to regulate prices.

Upon considerations of these recommendations, the final strategy would be to address all these recommendations before implementing a legal framework in Canada.

Appendices

Appendix 1. Summary of SAP Authorizations for January-December 2013 in eSAP

Summary of SAP Authorizations for January-December 2013 in eSAP

Product name	Number of requests Authorized
18f-fdopa (18f-fluorodopa)	1
3,4-diaminopyridine 10mg	92
714X (trimethylaminohydroxybicycloheptane chloride) 63mg/mL	21
ABT-333 250mg	1
ABT-450/ritonavir/ABT-267	1
Abthrax (raxibacumab) 50mg/mL	1
Acthrel (corticorelin ovine triflutate) 20µg/mL	25
ACTIMMUNE (interferon gamma-1b) 0.2mg/mL	42
Actiq (fentanyl citrate) 800µg	1
Adagen (pegademase bovine) 250IU/mL	16
Adcetris (brentuximab vedotin) 50mg	13
Additive Solution Formula 3	1
afatinib (BIBW 2992) 30mg	43
afatinib (BIBW 2992) 40mg	125
afatinib (BIBW2992) 50mg	41
Alinia (nitazoxanide) 500mg	28
Alinia (nitazoxanide) 1.2g	14
Ambien (zolpidem tartrate) 10mg	2
Ammonul (sodium phenylacetate and sodium benzoate)	29
Ammonul (sodium phenylacetate and sodium benzoate) 10% 10%	13
amoxapine 50mg	1
Anadrol-50 (oxymetholone) 50mg	3
Anafranil (clomipramine) 12.5mg/mL	8
Ancotil (flucytosine) 1%	12
Ancotil (flucytosine) 500mg	91
Andractim (androstanolone gel)	4
Antivipmyn (polyvalent equine anti-viper serum)	5
Apo-Cisapride (cisapride monohydrate) 10mg	494
AquADEKs Chewable Tablets	2
AquADEKs Pediatric Liquid	237
AquADEKs Softgels	226
AQUASOL A Parenteral (water-miscible vitamin A palmitate) 50000USPU/mL	1
Arcalyst (rilonacept) 220mg	27
Aristospan (triamcinolone hexacetonide) 20mg/mL	586
ARRY-334543 100mg	2
artesunate 110mg	2
AtroPen 2mg	3
atropine sulfate 1%	1
atropine sulphate 0.1mg/mL	1
atropine sulphate 2mg/mL	1
Aubagio (teriflunomide) 14mg	4
Azactam (aztreonam) 1g	215

aztreonam 1g	2
aztreonam 2g	1
Banocide (diethylcarbamazine) 50mg	19
Berotec HFA (fenoterol hydrobromide) 100µg	1
bicaVera 2.3%	19
bicaVera 4.25%	1
BioThrax (anthrax vaccine)	2
Biotin-8 (biotin) 8mg	43
black widow (latrodectus mactans) antivenin (equine) 6000U	11
Bosutinib (bosutinib) 100mg	18
Botulism Antitoxin Behring (botulism antitoxin type A, type B, and type E) 1(	20
Brevibloc (esmolol hydrochloride) 10mg/mL	25
Brevital Sodium (methohexital sodium) 500mg	139
Brolene (propamidine isethionate) 1mg/mL	33
Bumex (bumetanide) 0.5mg/mL	18
Buphenyl (sodium phenylbutyrate) 250g	11
Buphenyl (sodium phenylbutyrate) 500mg	5
Buphenyl (sodium phenylbutyrate) 250g	56
Buphenyl (sodium phenylbutyrate) 500mg	36
caffeine citrate 10mg/mL - Sandoz	342
caffeine citrate 20mg/mL - Sagent	1
Calcium Gluconate 10% (W/V)	24
Calcort (deflazacort) 6mg	318
Capastat Sulfate (capreomycin) 1g	1
Carbaglu (carglumic acid) 200mg	22
Cardene IV (nicardipine hydrochloride) 0.1mg/mL	10
Cardene IV (nicardipine hydrochloride) 0.2mg/mL	12
Catapres (clonidine hydrochloride) 150µg/mL	68
Catapres (clonidine hydrochloride) 0.1mg	1
Catapres (clonidine hydrochloride) 0.2mg	9
Celontin (methsuximide) 300mg	45
Ceprotin (protein c concentrate) 1000IU	2
Ceprotin (protein c concentrate) 500IU	7
Chemet (succimer) 100mg	19
ChiRhoStim (synthetic human secretin) 16µg	24
chlorothiazide sodium 0,5g	8
cidofovir 75mg/mL	43
cilengitide 8mg/mL	3
cilostazol 100mg	18
Clopine (clozapine) 50mg/mL	1
Clorpactin WCS-90 (sodium oxychlorosene) 2g	10
CMX-001	1
cobicistat 150mg	11
Cometriq (cabozantinib) 20mg	1
Cometriq (cabozantinib) 80mg	1
Corlopam (fenoldopam mesylate) 10mg/mL	1
Cortef (hydrocortisone) 5mg	13

Cortirel (corticorelin) 100µg	2
Coumadin (warfarin sodium) 5mg	2
CroFab (crotalidae polyvalent immune fab (ovine)) 1g	10
Cyclomydril (clyclopentolate HCl and phenylephrine HCl)	62
Cyclomydril (cyclopentolate HCl and phenylephrine HCl)	12
Cystagon (cysteamine bitartrate) 150mg	114
Cystagon (cysteamine bitartrate) 50mg	70
D3-Vicotrat (cholecalciferol)	1
dabrafenib 50mg	3
dabrafenib 75mg	2
Dacogen (decitabine) 50mg	4
DAS181 13mg	2
Decuprate (bis-choline tetrathiomolybdate) 30mg	3
defibrotide 200mg	33
Demerol (meperidine) 50mg/mL	26
Demser (metyrosine) 250mg	5
Depacon (valproate sodium) 100mg/mL - Abbott	62
Depacon (valproate sodium) 100mg/mL - AbbVie	102
Depakote Sprinkle Capsules (divalproex sodium) 125mg - Abbott	78
Depakote Sprinkle Capsules (divalproex sodium) 125mg - Abbvie	168
DepoCyt (cytarabine) 10mg/mL	4
dextrose 10% in 0.2% chloride	19
Diacomit (stiripentol) 250mg	36
Diacomit (stiripentol) 500mg	7
Diamox SR (acetazolamide) 250mg	1
Diaphin (diamorphine hydrochloride)	20
Diazepam Autoinjector (diazepam usp) 5mg/mL	4
Dibenzyline (phenoxybenzamine hydrochloride) 10mg	84
Dimaval (DMPS) 100mg	1
Dimaval (DMPS) 50mg/mL	1
Ditripentat-Heyl (calcium trisodium pentetate) 0.2g/mL	1
Dodecavit (hydroxocobalamin acetate) 5mg/mL	24
Dogmatil (sulpiride) 200mg	239
dolutegravir 50mg	8
dopamine hydrochloride 40mg/mL	19
doxycycline hyclate 5mg/mL	147
DuoDote (atropine and pralidoxime chloride)	6
Durezol (difluprednate) 0.05%	2
edetate calcium disodium 5%	11
Edronax (reboxetine methanesulfonate) 4mg	17
Emgrast-M (sargramostim) 500µg	2
Enlon (edrophonium chloride) 10mg/mL	20
ENMD-2076 225mg	1
enzalutamide (MDV-3100) 40mg	11
epinephrine hydrochloride 1mg/mL	1
Epogen (epoetin alfa) 20000U/mL	2
etomidate 2mg/mL	30

etomidate injection 2mg/mL	3
Etomidate-Lipuro 2mg/mL	567
Etopophos (etoposide phosphate) 100mg	53
Excegran (zonisamide) 100mg	22
F-18 Fluorodeoxyglucose	1
Factor VII Concentrate (human coagulation factor VII) 600IU	41
Factor X P Behring (human coagulation factor IX and X)	2
Factor XI Concentrate (human coagulation factor XI) 1000IU	25
Fareston (toremifene citrate) 60mg	3
Fasigyn (tinidazole) 500mg	21
Fasinex (triclabendazole) 250mg	2
Felbatol (felbamate) 120mg/mL	6
Felbatol (felbamate) 600mg	104
Ferriprox (deferiprone) 500mg	99
Fibrogammin P (human coagulation factor XIII) 1250IU	30
Fibrogammin P (human coagulation factor XIII) 250IU	118
Firazyr (icatibant acetate) 10mg/mL	24
floxuridine 500mg	3
Folotyn (pralatrexate) 40mg/mL	1
Foscavir (foscarnet trisodium hexahydrate) 24mg/mL	197
Fosfocina (sodium fosfomycin)	2
Freeze-Dried Glutamate BCG vaccine	5
Fucidin (sodium fusidate) 250mg	29
Fycompa (perampanel) 12mg	6
Fycompa (perampanel) 4mg	5
Fycompa (perampanel) 6mg	2
Gabitril (tiagabine hydrochloride) 16mg	2
Gabitril (tiagabine hydrochloride) 4mg	5
Galzin (zinc acetate) 25mg	1
Galzin (zinc acetate) 50mg	11
Gattex (teduglutide) 5mg	1
gentamicin- preservative free 10mg/mL	1
Glycophos (Sodium Glycerophosphate)	20
Glypressin (terlipressin acetate) 1mg	1
Gonapeptyl depot (triptorelin) 3.75mg	2
guanethidine monosulphate 10mg/mL	5
guanfacine hydrochloride 1mg	98
guanidine hydrochloride 125mg	4
Haemocomplettan P (fibrinogen) 1g	7
Hemofil M (antihemophilic factor (human), factor viii) 1000IU	2
Hemopure (hemoglobin glutamer-250 (bovine))	1
heptavalent botulism antitoxin (equine) 7500U	1
Humulin R (regular human insulin) 500U/mL	133
Hyalase (hyaluronidase) 1500IU	61
Hycamtin (topotecan hydrochloride) 1mg	1
hydroxocobalamin acetate 1mg/mL	69
HyperRHO S/D Full Dose (Rho(D) human immune globulin) 1500IU	4

Hypurin Bovine Lente (bovine insulin zinc suspension) 100IU/mL	10
Hypurin Bovine Neutral (neutral bovine insulin) 100IU/mL	9
Hypurin Bovine Protamine Zinc (protamine zinc bovine insulin) 100IU/mL	3
I-123 MIBG	15
I-131 MIBG	80
I-131 sodium o-iodohippurate 250MBq	1
Ikorel (nicorandil) 10mg	317
Ilomedin (iloprost trometamol) 13.4µg/mL	3
Ilomedin (iloprost trometamol) 33.5µg/mL	13
Impavido (miltefosine) 50mg	2
Increlex (mecasermin) 10mg/mL	4
Indolar SR (indometacin) 75mg	1
indomethacin for injection 1mg	41
inotuzumab ozogamicin 3.5mg	1
IPI-504	1
Istodax (romidepsin) 10mg	44
Isuprel (isoproterenol hydrochloride) 0.2mg/mL	1
Jetrea (ocriplasmin) 2.5mg/mL	6
Kalydeco (ivacaftor) 150mg	2
Kit for the preparation of Technetium Tc99m Mebrofenin	198
KOATE-DVI (Antihemophilic factor (human)) 250IU	1
K-Phos Neutral 250mg	22
K-phos No.2	8
K-phos Original	1
Krystexxa (pegloticase) 8mg/mL	2
Lafepe Benznidasol 100mg	3
Lamprene (clofazimine) 50mg	72
L-citrulline 600mg	7
LDK378 150mg	7
Leukine (sargramostin powder) 250µg	22
Leukine (sargramostin) 500µg/mL	1
levetiracetam 100mg/mL	3
Lexiscan (regadenoson) 0.08mg/mL	24
Lodosyn (carbidopa) 25mg	41
Lorenzo's Oil	1
Lullan (perospirone) 8mg	2
LuMark (Lu-177 trichloride)	67
Lumitene (beta-carotene) 30mg	6
Mag-tab SR 84mg	3
Marplan (isocarboxazid) 10mg	1
Mectizan (ivermectin) 3mg	330
Medical Maggots	21
medicinal leeches	120
Mephyton (phytonadione) 5mg	42
mepolizumab (SB-240563) 250mg	1
Mestinon (pyridostigmine bromide) 12mg/mL	3
Metanor (flupirtine maleate) 100mg	2

Metopirone (metyrapone) 250mg	21
metreleptin 11mg	2
midostaurin (PKC412) 25mg	4
Mifeprex (mifepristone) 200mg	2
Mifepristone Linepharma 200mg	1
monoclonal antibody chimeric 14.18 5mg/mL	4
motesanib 25mg	2
Mustargen (Mechlorethamine hydrochloride)	1
Mylotarg (gemituzumab ozogamicin) 5mg	3
Mytelase (ambenonium chloride) 10mg	3
Naglazyme (galsulfase) 1mg/mL	18
Natacyn (natamycin) 5%	21
Nembutal Sodium Solution (pentobarbital sodium) 50mg/mL	76
Nesacaine - MPF 2% (chloroprocaine HCl - preservative free) 20mg/mL	33
nifurtimox 120mg	1
Nimoral (Nimorazole)	2
Nimoral (Nimorazole) 500mg	4
Nipent (pentostatin) 10mg	16
niraparib	3
Norchol-131 (I-131 iodomethyl norcholesterol)	4
Normosang (human hemin) 25mg/mL	13
Northera (droxidopa) 200mg	1
Notezine (diethylcarbamazine) 100mg	3
Nulojix (Belatacept) 250mg	5
Nydrazid (isoniazid) 100mg/mL	57
obinutuzumab 25mg/mL	1
omacetaxine mepesuccinate 3.5mg	6
Omegaven (fish oil) 0.1g/mL	245
Oncaspar (pegaspargase) 750IU/mL	258
Oral transmucosal fentanyl citrate 800µg	1
Orfadin (nitisinone) 10mg	15
Orfadin (nitisinone) 2mg	27
Orfadin (nitisinone) 5mg	9
Ospolot (sulthiame) 200mg	5
Ospolot (sulthiame) 50mg	65
Oxandrin (oxandrolone) 10mg	7
Oxandrin (oxandrolone) 2.5mg	13
P32 chromic phosphate 5mCi/mL	1
P-32 sodium orthophosphate	12
Panhematin (hemin)	18
paraldehyde	1
Paser (aminosalicyclic acid) 4g	17
pasireotide (SOM230B) 0.6mg/mL	4
pasireotide (SOM230B) 0.9mg/mL	1
Peak K2 (menatetrenone mk-4) 15mg	4
Pedea (ibuprophen) 5mg/mL	47
Pentostam (sodium stibogluconate) 100mg/mL	1

pertuzumab 30mg/mL	1
Phospholine Iodide (echothophate iodide) 0,125%	8
physostigmine salicylate 1mg/mL	88
phytonadione 2mg/mL	3
Picato (ingenol mebutate) 0.05%	1
Picibanil (OK-432) 0.02mg	30
Picibanil (OK-432) 0.1mg	13
Piracetam EG 1200mg	37
Pixuvri (pixantrone) 29mg	1
Platinol (cisplatin) 50mg	16
Polidocanol (aethoxysclerol) 1%	8
Polidocanol (aethoxysclerol) 3%	6
pomalidomide 1mg	3
pomalidomide 2mg	296
pomalidomide 3mg	2
ponatinib 15mg	76
potassium chloride	52
Previscan (fluindione) 20mg	1
probenecid 500mg	18
Proglycem (diazoxide) 50mg/mL	111
Proluton Depot (hydroxyprogesterone caproate) 250mg/mL	10
Protopam Chloride (pralidoxime chloride) 1g	41
Pyridostigmine Bromide 30mg	1
quinidine gluconate 80mg/mL	1
Quinidine Sulfate 200mg	25
Quinidine Sulfate 300mg	19
Quininject (quinine dihydrochloride) 300mg/mL	1
Qutenza (capsaicin) 8%	2
Radiogardase (prussian blue) 0.5g	3
Ranexa (ranolazine) 1000mg	2
Ranexa (ranolazine) 500mg	17
regorafenib 40mg	17
Relenza (zanamivir) 10mg/mL	10
RENOCIS (DMSA)	22
Renvela (sevelamer carboante powder) 2.4g	23
Reolysin	2
retaspimycin hydrochloride (IPI-504) 844.5mg	1
R-Gene 10 (arginine hydrochloride) 10%	3
Ribasphere (ribavirin) 200mg	1
Rifadin (rifampin) 600mg	128
RYTHMODAN (Disopyramide) 100mg	42
Rythmol (propafenone hydrochloride) 10mg	6
Rythmol (propafenone hydrochloride) 3.5mg/mL	2
Saflutan (tafluprost) 15µg/mL	25
Samyr (ademetionine sulphate tosylate) 400mg	6
Sandimmune (cyclosporine) 100mg	6
Sandimmune (cyclosporine) 25mg	21

Sandimmune (cyclosporine) 100mg/mL	7
Sclerosol Intrapleural Aerosol (talc) 4g	18
Seromycin (cycloserine) 250mg	21
simeprevir 150mg	1
Sirdalud MR (tizanidine) 6mg	2
Sirturo (bedaquiline) 100mg	2
SMOFlipid	8
Sodium Diuril (chlorothiazide sodium) 0.5g	6
sodium nitrite 30mg/mL	6
sodium phosphate USP 3mmol/mL	1
sodium thiosulfate 250mg/mL	23
sofosbuvir 400mg	19
Solian (amisulpride) 100mg	42
Solian (amisulpride) 400mg	60
Soludactone (potassium canrenoate) 100mg	3
Soma (carisoprodol) 350mg	2
SourceCF Chewables	3
SourceCF Pediatric Drops	1
SourceCF Softgels	2
Speciality Amino Acid Solution	5
Stablon (tianeptine sodium) 12,5mg	8
Sterile Talc Powder (talc) 5g	44
Steritalc (large size sterile talc powder) 4g	6
Sterogyl 15 "H" (ergocalciferol) 600000IU/1.5 mL	25
Subutex Sublingual Tablets (buprenorphine hydrochloride) 2mg	68
Subutex Sublingual Tablets (buprenorphine hydrochloride) 400µg	5
Subutex Sublingual Tablets (buprenorphine hydrochloride) 8mg	71
Sucraid (sacrosidase) 8500IU/mL	14
sulfadiazine 500mg	44
sulfamethoxazole and trimethoprim	3
Sulfamylon (mafenide acetate) 50g	23
Sulfamylon Cream (mafenide acetate cream) 2OZ	21
Sulfamylon Cream (mafenide acetate cream) 4OZ	2
Sustiva (efavirenz) 30mg/mL	3
Synastone (methadone hydrochloride) 10mg/mL - 1mL Ampoule(s)	45
Synastone (methadone hydrochloride) 50mg/mL - 1mL Ampoule(s)	23
Synastone (methadone hydrochloride) 10mg/mL - 5mL Ampoule(s)	2
Synercid (quinupristin and dalfopristin)	6
Syprine (trientine hydrochloride) 250mg	118
Targretin (bexarotene) 1% - Eisai Inc.	2
Targretin (bexarotene) 75mg - Eisai Inc.	10
Targretin (bexarotene) 1% - Valeant	1
Targretin (bexarotene) 75mg - Valeant	7
Tasmar (tolcapone) 100mg	21
Taurolin (taurolidine) 2%	14
Teflaro (ceftaroline fosamil) 600mg	8
Tepadina (thiotepa) 100mg	67

Tepadina (thiotepa) 15mg	30
Testred C III (methyltestosterone) 10mg	2
Thiola (tiopronin) 100mg	75
thioridazine hydrochloride, USP 25mg	22
Thyrel (protirelin) 0.2mg/mL	23
Tiapride (tiapridal) 100mg	1
Tikosyn (dofetilide) 125µg	176
Tikosyn (dofetilide) 250µg	259
Tikosyn (dofetilide) 500µg	221
Tilade CFC-free inhaler (nedocromil sodium)	1
Timoptic (timolol maleate) 0.5%	57
trastuzumab emtansine (T-DM1) 160mg	56
Travatan (travoprost ophthalmic solution) 0.004%	3
Trecator (ethionamide) 250mg	16
Treosulfan (treosulfan) 5g	1
triCitrasol (trisodium citrate) 46,7%	4
Triostat (liothyronine sodium) 10µg/mL	1
Tript-OH (L-5-hydroxytryptophan) 100mg	4
Tript-OH (L-5-hydroxytryptophan) 50mg	7
Tript-OH (L-5-hydroxytryptophan) 25mg	2
Trisenox (arsenic trioxide) 1mg/mL	75
trisodium zinc pentetate (Zn-DTPA) 211mg/mL	1
Trobicin (spectinomycin hydrochloride) 2g	4
Twinlab Liqui-E (water soluble vitamin E)	21
Ultracain D (epinephrine free) (articaine hydrochloride) 40mg/mL	1
Unasyn 3g	1
uridine triacetate 250g	1
Uvadex (methoxsalen) 2µg/mL	76
Valdoxan (agomelatine) 25mg	40
Vastarel (trimetazidine) 35mg	2
Ventavis (iloprost) 10µg/mL	3
Vercyte (pipobroman) 25mg	11
Videx (didanosine) 4g	4
Viibryd (vilazodone) 10mg	1
Viramune (nevirapine hemihydrate) 10mg/mL	84
Virazole (ribavirin) 0.1g/mL	18
VIREAD (tenofovir disoproxil furamate) 250mg	2
Virgan (ganciclovir) 0.15%	2
vismodegib 150mg	3
Vistide (cidofovir) 75mg/mL	46
Vitamin E (alpha-tocopherol acetate) 100mg/2 mL	2
Viviant (bazedoxifene) 20mg	3
voclosporin 10mg	3
voclosporin 5mg	3
VoLumen (barium sulfate) 0.1%	1
Voraxaze (glucarpidase) 1000U	12
Wellbutrin Ir (buproprion) 75mg	1

Wycillin (penicillin g procaine suspension) 1200000U	1
Xenbilox (chenodeoxycholic acid) 250mg	9
Xifaxan (rifaximin) 550mg	770
Yttrium-90 Citrate CIS Bio International	2
Zaltrap (aflibercept) 25mg/mL	2
Zanosar (streptozocin) 1g	34
Zemplar (paricalcitol) 5µg/mL	3
Zentel (albendazole) 200mg	1
Zentel (albendazole) 400mg	212
Zerit (stavudine) 200mg	6
Zonegran (zonisamide) 100mg	44
Zonegran (zonisamide) 50mg	6
Zovirax (acyclovir) 3%	159

Appendix 2. Compiled data from SAP drugs with an orphan drug designation, either by the Orphanet or the FDA database

Summary of SAP Authorizations for January-December 2013 in eSAP						
Product name	**Alternative name**	**Dose**	**Orphan designation**	**Orphan designation**	**Orpha number**	**Number of requests Authorized**
						14532
18f-fdopa	18f-fluorodopa					1
3,4-diaminopyridine		10mg	USA	Europe	ORPHA82347	92
714X	trimethylamino hydroxybicyclo heptane chloride	63mg/ml				21
ABT-333		25mg				1
ABT-450	ritonavir, ABT-267					1
Abthrax	raxibacumab	50mg/ml		Europe	ORPHA410394	1
Acthrel	corticorelin ovine triflutate	20µg/ml	USA			25
ACTIMMUNE	interferon gamma-1b	0.2mg/ml	USA			42
Actiq	fentanyl citrate	800µg				1
Adagen	pegademase bovine	2501U/ml	USA		ORPHA100845	16
Adcetris	brentuximab vedotin	50mg	USA	Europe	Europe: ORPHA299952 USA: ORPHA398790	13
Additive Solution Formula 3						1
afatinib	BIBW 2992	30mg	USA		USA: ORPHA413782	43
afatinib	BIBW 2992	40mg	USA		USA: ORPHA413782	125
afatinib	BIBW 2992	50mg	USA		USA: ORPHA413782	41
Alinia	nitazoxanide	500mg	USA		ORPHA34106	28

Alinia	nitazoxanide	1,2g	USA		ORPHA34106	14
Ambien	zolpidem tartrate	10mg				2
Ammonul	sodium phenylacetate and sodium benzoate		USA		ORPHA87861	29
Ammonul	sodium phenylacetate and sodium benzoate	10%	USA		ORPHA87861	13
amoxapine		50mg				1
Anadrol-50	oxymetholone	50mg				3
Anafranil	clomipramine	12,5mg/ml				8
Ancotil	flucytosine	1%				12
Ancotil	flucytosine	500mg				91
Andractim (androstanolone gel)						4
Antivipmyn (polyvalent equine anti-viper serum)						5
Apo-Cisapride	cisapride monohydrate	10mg				494
AquADEKs Chewable Tablets						2
AquADEKs Pediatric Liquid						237
AquADEKs Softgels						226
AQUASOL A Parenteral (water-miscible vitamin A palmitate)		50000USPU/ml				1
Arcalyst	rilonacept	220mg	USA	Europe	ORPHA95344	27
Aristospan	triamcinolone hexacetonide	20mg/ml				586

ARRY-334543		100mg				2
artesunate		110mg	USA	Europe	ORPHA88970	2
AtroPen		2mg				3
atropine sulfate		1%				1
atropine sulphate		0,1mg/ml				1
atropine sulphate		2mg/ml				1
Aubagio	teriflunomide	14mg				4
Azactam	aztreonam	1g	USA	Europe	ORPHA83687	215
aztreonam		1g	USA	Europe	ORPHA83687	2
aztreonam		2g	USA	Europe	ORPHA83687	1
Banocide	diethylcarbamazine	50mg				19
Berotec HFA	fenoterol hydrobromide	100µg				1
bicaVera		2,30%				19
bicaVera		4,25%				1
BioThrax (anthrax vaccine)						2
Biotin-8		8mg				43
black widow antivenin (equine)	latrodectus mactans	6000U				11
Bosutinib		100mg	USA	Europe	ORPHA229458	18
Botulism Antitoxin Behring (botulism antitoxin type A, type B, and type E) 10?			USA		ORPHA405648	20
Brevibloc	esmolol hydrochloride	10mg/ml				25
Brevital Sodium	methohexital sodium	500mg				139

Brolene	propamidine isethionate	1mg/ml				33
Bumex	bumetanide	0,5mg/ml				18
Buphenyl	sodium phenylbutyrate	250mg	USA	Europe	ORPHA25062	11
Buphenyl	sodium phenylbutyrate	500mg	USA	Europe	ORPHA25062	5
Buphenyl	sodium phenylbutyrate	250mg	USA	Europe	ORPHA25062	56
Buphenyl	sodium phenylbutyrate	500mg	USA	Europe	ORPHA25062	36
caffeine citrate - Sandoz		10mg/ml		Europe	ORPHA133569	342
caffeine citrate - Sagent		20mg/ml		Europe	ORPHA133569	1
Calcium Gluconate		10%				24
Calcort	deflazacort	6mg				318
Capastat Sulfate	capreomycin	1g				1
Carbaglu	carglumic acid	200mg	USA	Europe	ORPHA35161	22
Cardene IV	nicardipine hydrochloride	0,1mg/ml				10
Cardene IV	nicardipine hydrochloride	0,2mg/ml				12
Catapres	clonidine hydrochloride	150µg/ml		Europe	ORPHA275660	68
Catapres	clonidine hydrochloride	0,1mg/ml		Europe	ORPHA275660	1
Catapres	clonidine hydrochloride	0,2mg/ml		Europe	ORPHA275660	9
Celontin	methsuximide	300mg				45
Ceprotin (protein c concentrate)		1000IU	USA		ORPHA24899	2
Ceprotin (protein c concentrate)		500IU	USA		ORPHA24899	7
Chemet	succimer	100mh	USA			19

ChiRhoStim (synthetic human secretin)		16µg				24
chlorothiazide sodium		0,5g				8
cidofovir		75mg/ml				43
cilengitide		8mg/ml	USA		ORPHA81687	3
cilostazol		100mg				18
Clopine	clozapine	50mg/ml				1
Clorpactin WCS-90	sodium oxychlorosene	2g				10
CMX-001						1
cobicistat		150mg				11
Cometriq	cabozantinib	20mg	USA		ORPHA394243	1
Cometriq	cabozantinib	80mg	USA		ORPHA394243	1
Corlopam	fenoldopam mesylate	10mg/ml				1
Cortef	hydrocortisone	5mg			ORPHA352511	13
Cortirel	corticorelin	100µg	USA			2
Coumadin	warfarin sodium	5mg				2
CroFab (crotalidae polyvalent immune fab (ovine))		1g				10
Cyclomydril	clyclopentolate HCl and phenylephrine HCl					62
Cyclomydril	clyclopentolate HCl and phenylephrine HCl					12
Cystagon	cysteamine bitartrate	150mg	USA		ORPHA24962	114

Cystagon	cysteamine bitartrate	50mg	USA		ORPHA24962	70
D3-Vicotrat	cholecalciferol		N/A		ORPHA371794	1
dabrafenib		50mg				3
dabrafenib		75mg/ml				2
Dacogen	decitabine	50mg	USA	Europe	ORPHA77330	4
DAS181		13mg				2
Decuprate	bis-choline tetrathiomolybdate	30mg			ORPHA414762	3
defibrotide		200mg	USA	Europe	ORPHA85388	33
Demerol	meperidine	50mg/ml				26
Demser	metyrosine	250mg				5
Depacon - Abbott	valproate sodium	100mg/ml				62
Depacon - AbbVie	valproate sodium	100mg/ml				102
Depakote Sprinkle Capsules - Abbott	divalproex sodium	125mg				78
Depakote Sprinkle Capsules - Abbvie	divalproex sodium	125mg				168
DepoCyt	cytarabine	10mg/ml	N/A		ORPHA45976	4
dextrose		10% in 0,2% chloride				19
Diacomit	stiripentol	250mg		Europe	ORPHA41778	36
Diacomit	stiripentol	500mg		Europe	ORPHA41778	7
Diamox SR	acetazolamide	250mg				1
Diaphin	diamorphine hydrochloride					20
Diazepam Autoinjector	diazepam usp	5mg/ml				4

Dibenzyline	phenoxybenzamine hydrochloride	10mg				84
Dimaval	DMPS	100mg				1
Dimaval	DMPS	50mg/ml				1
Ditripentat-Heyl	calcium trisodium pentetate	0,2g/ml				1
Dodecavit	hydroxocobalamin acetate	5mg/ml				24
Dogmatil	sulpiride	200mg				239
dolutegravir		50mg				8
dopamine hydrochloride		40mg/ml				19
doxycycline hyclate		5mg/ml		Europe	ORPHA35266	147
DuoDote	atropine and pralidoxime chloride					6
Durezol	difluprednate	0,05%	USA		ORPHA394517	2
edetate calcium disodium		5%				11
Edronax	reboxetine methanesulfonate	4mg				17
Emgrast-M	sargramostim	500µg				2
Enlon	edrophonium chloride	10mg/ml				20
ENMD-2076		225mg				1
enzalutamide	MDV-3100	40mg				11
epinephrine hydrochloride		1 mg/ml				1
Epogen	epoetin alfa	20000U/ml				2
etomidate		2mg/ml				30
etomidate injection		2mg/ml				3

Etomidate-Lipuro		2mg/ml				567
Etopophos	etoposide phosphate	100 mg				53
Excegran	zonisamide	100 mg				22
F-18 Fluorodeoxyglucose						1
Factor VII Concentrate (human coagulation factor VII)		600IU				41
Factor X P Behring (human coagulation factor IX and X)						2
Factor XI Concentrate (human coagulation factor XI)		1000IU				25
Fareston	toremifene citrate	60mg	USA			3
Fasigyn	tinidazole	500mg	USA		ORPHA57037	21
Fasinex	triclabendazole	250mg				2
Felbatol	felbamate	120mg/ml	USA		ORPHA24982	6
Felbatol	felbamate	600mg	USA		ORPHA24982	104
Ferriprox	deferiprone	500mg	USA	Europe	ORPHA42568	99
Fibrogammin P (human coagulation factor XIII)		1250IU				30
Fibrogammin P (human coagulation factor XIII)		250IU				118
Firazyr	icatibant acetate	10mg/ml	USA	Europe	ORPHA82439	24

floxuridine		500mg				3
Folotyn	pralatrexate	40mg/ml	USA	Europe	ORPHA90183	1
Foscavir	foscarnet trisodium hexahydrate	24mg/ml				197
Fosfocina	sodium fosfomycin					2
Freeze-Dried Glutamate BCG vaccine						5
Fucidin	sodium fusidate	250mg				29
Fycompa	perampanel	12mg				6
Fycompa	perampanel	4mg				5
Fycompa	perampanel	6mg				2
Gabitril	tiagabine hydrochloride	16mg				2
Gabitril	tiagabine hydrochloride	4mg				5
Galzin	zinc acetate	25mg	USA		ORPHA56897	1
Galzin	zinc acetate	50mg	USA		ORPHA56897	11
Gattex	teduglutide	5mg	USA	Europe	ORPHA101257	1
gentamicin-preservative free		10 mg/mL				1
Glycophos	Sodium Glycerophosphate					20
Glypressin	terlipressin acetate	1 mg				1
Gonapeptyl depot	triptorelin	3,75mg				2
guanethidine monosulphate		10 mg/mL				5
guanfacine hydrochloride		1 mg				98
guanidine hydrochloride		125mg				4

Haemocomplettan P	fibrinogen	1 g			ORPHA131045	7
Hemofil M (antihemophilic factor (human), factor VIII)		1000IU				2
Hemopure (hemoglobin glutamer-250 (bovine))						1
heptavalent botulism antitoxin (equine)		7500U	USA		ORPHA405648	1
Humulin R (regular human insulin)		500U/ml				133
Hyalase	hyaluronidase	1500IU				61
Hycamtin	topotecan hydrochloride	1 mg			ORPHA131290	1
hydroxocobalamin acetate		1 mg/ml				69
HyperRHO S/D Full Dose (Rho(D) human immune globulin)		1500IU				4
Hypurin Bovine Lente (bovine insulin zinc suspension)		1001U/mL				10
Hypurin Bovine Neutral (neutral bovine insulin)		1001U/mL				9
Hypurin Bovine Protamine Zinc (protamine zinc bovine insulin)		1001U/mL				3
I-123 MIBG						15
I-131 MIBG						80
I-131 sodium o-iodohippurate		250MBq				1

Ikorel	nicorandil	10mg				317
Ilomedin	iloprost trometamol	13,4µg/mL			ORPHA103178	3
Ilomedin	iloprost trometamol	33,5 µg/mL			ORPHA103178	13
Impavido	miltefosine	50mg	USA	Europe	ORPHA65974	2
Increlex	mecasermin	10mg/mL	USA	Europe		4
Indolar SR	indometacin	75mg				1
indomethacin for injection		1 mg				41
inotuzumab ozogamicin		3,5mg		Europe	ORPHA282211	1
IPL-504	retaspimycin hydrochloride?					1
Istodax	romidepsin	10mg	USA			44
Isuprel	isoproterenol hydrochloride	0,2mg/mL				1
Jetrea	ocriplasmin	2,5mg/mL				6
Kalydeco	ivacaftor	150mg	USA	Europe	ORPHA139922	2
Kit for the preparation of Technetium Tc99m Mebrofenin						198
KOATE-DVI (Antihemophilic factor (human))		250IU				1
K-Phos Neutral		250mg				22
K-phos No.2						8
K-phos Original						1
Krystexxa	pegloticase	8mg/mL	USA			2
Lafepe Benznidazol		100mg				3

Lamprene	clofazimine	50 mg	USA		ORPHA24950	72
L-citrulline		600mg				7
LDK378		150mg				7
Leukine	sargramostin powder	250µg	USA			22
Leukine	sargramostin	500µg/mL	USA			1
levetiracetam		100mg/mL				3
Lexiscan	regadenoson	0,08mg/mL				24
Lodosyn	carbidopa	25mg				41
Lorenzo's Oil						1
Lullan	perospirone	8mg				2
LuMark	Lu-177 trichloride					67
Lumitene	beta-carotene	30mg				6
Mag-tab SR		84mg				3
Marplan	isocarboxazid	10mg				1
Mectizan	ivermectin	3mg				330
Medical Maggots						21
medicinal leeches						120
Mephyton	phytonadione	5mg				42
mepolizumab	SB-240563	250mg	USA	Europe	ORPHA84164	1
Mestinon	pyridostigmine bromide	12mg/mL				3
Metanor	flupirtine maleate	100mg				2
Metopirone	metyrapone	250mg				21
metreleptin		11mg	USA	Europe	ORPHA300654	2
midostaurin	PKC412	25mg	USA	Europe	ORPHA66150	4

Mifeprex	mifepristone	200mg				2
Mifepristone Linepharma		200mg				1
monoclonal antibody chimeric 14.18		5mg/ml				4
motesanib		25mg				2
Mustargen	Mechlorethamine hydrochloride					1
Mylotarg	gemituzumab ozogamicin	5mg	USA	Europe	ORPHA42780	3
Mytelase	ambenonium chloride	10mg				3
Naglazyme	galsulfase	1 mg/ml	USA		ORPHA65852	21
Natacyn	natamycin	5%				76
Nembutal Sodium Solution	pentobarbital sodium	50mg/ml				33
Nesacaine - MPF 2%	chloroprocaine HCl - preservative free	20mg/ml				1
nifurtimox		120mg				2
Nimoral	Nimorazole			Europe	ORPHA24584	4
Nimoral	Nimorazole	500mg		Europe	ORPHA24584	16
Nipent	pentostatin	10mg	USA			3
niraparib						4
Norchol-131	I-131 iodomethyl norcholesterol					13
Normosang (human hemin)		25mg/ml		Europe	ORPHA25128	1
Northera	droxidopa	200mg	USA		ORPHA393911	3
Notezine	diethylcarbamazine	100mg				5
Nulojix	Belatacept	250mg	USA			57

Nydrazid	isoniazid	100mg/ml				1
obinutuzumab		25mg/ml	USA	Europe	ORPHA317257	6
omacetaxine mepesuccinate	Synribo	3,5mg	USA		ORPHA368193	245
Omegaven (fish oil)		0,1g/ml				258
Oncaspar	pegaspargase	750IU/ml	USA		ORPHA25045	1
Oral transmucosal fentanyl citrate		800µg				15
Orfadin	nitisinone	10mg	USA	Europe	ORPHA56899	27
Orfadin	nitisinone	2mg	USA	Europe	ORPHA56899	9
Orfadin	nitisinone	5mg	USA	Europe	ORPHA56899	5
Ospolot	sulthiame	200mg				65
Ospolot	sulthiame	50mg				7
Oxandrin	oxandrolone	10mg				13
Oxandrin	oxandrolone	2,5mg				1
P32 chromic phosphate		5mCi/mL				12
P-32 sodium orthophosphate						18
Panhematin (hemin)			USA		ORPHA24990	1
paraldehyde						17
Paser	aminosalicyclic acid	4g	USA		ORPHA24936	4
pasireotide	SOM230B	0,6mg/ml		Europe	ORPHA101429	1
pasireotide		0,9mg/ml		Europe	ORPHA101429	4
Peak K2	menatetrenone mk-4	15mg				47
Pedea	ibuprophen	5mg/ml				1
Pentostam	sodium stibogluconate	100mg/ml				1

pertuzumab		30mg/ml				8
Phospholine Iodide	echothophate iodide	0,13%				88
physostigmine salicylate		1 mg/ml				3
phytonadione		2mg/ml				1
Picato	ingenol mebutate	0,05%				30
Picibanil	OK-432	0,02mg				13
Picibanil	OK-432	0,1mg				37
Piracetam EG		1200mg				1
Pixuvri	pixantrone	29mg				16
Platinol	cisplatin	50mg				8
Polidocanol	aethoxysclerol	1%				6
Polidocanol	aethoxysclerol	3%				3
pomalidomide		1 mg	USA	Europe	ORPHA201839	296
pomalidomide		2mg	USA	Europe	ORPHA201839	2
pomalidomide		3mg	USA	Europe	ORPHA201839	76
ponatinib		15mg	USA	Europe	ORPHA216911	52
potassium chloride						1
Previscan	fluindione	20mg				18
probenecid		500mg				111
Proglycem	diazoxide	50mg/ml	USA		ORPHA403944	10
Proluton Depot	hydroxyprogesterone caproate	250mg/ml				41
Protopam Chloride	pralidoxime chloride	1 g				1
Pyridostigmine Bromide		30mg				1
quinidine gluconate		80mg/ml				25

Quinidine Sulfate		200mg				19
Quinidine Sulfate		300mg				1
Quininject	quinine dihydrochloride	300mg/ ml				2
Qutenza	capsaicin	8%	USA			3
Radiogardase	prussian blue	0,5g	USA			2
Ranexa	ranolazine	1000mg				17
Ranexa	ranolazine	500mg				17
regorafenib		40mg	USA		ORPHA331088	10
Relenza	zanamivir	10mg/ml				22
RENOCIS	DMSA					23
Renvela	sevelamer carboante powder	2,4g				2
Reolysin						1
retaspimycin hydrochloride	IPI-504	844,5mg				3
R-Gene 10	arginine hydrochloride	10%				1
Ribasphere	ribavirin	200mg				128
Rifadin	rifampin	600mg	USA		ORPHA25051	42
RYTHMODAN	Disopyramide	100mg				6
Rythmol	propafenone hydrochloride	10mg				2
Rythmol	propafenone hydrochloride	3,5mg/m l				25
Saflutan	tafluprost	15µg/ml				6
Samyr	ademetionine sulphate tosylate	400mg				6
Sandimmune	cyclosporine	100mg				6
Sandimmune	cyclosporine	25mg				21
Sandimmune	cyclosporine	100mg/ ml				7

Sclerosol Intrapleural Aerosol	talc	4g	USA			18
Seromycin	cycloserine	250mg				21
simeprevir		150mg				1
Sirdalud MR	tizanidine	6mg				2
Sirturo	bedaquiline	100mg	USA	Europe	ORPHA394232	2
SMOFlipid						8
Sodium Diuril	chlorothiazide sodium	0,5g				6
sodium nitrite		30mg/ml		Europe	ORPHA299525	6
sodium phosphate USP		3mmol/ ml				1
sodium thiosulfate		250mg/ ml	USA	Europe	ORPHA237352	23
sofosbuvir		400mg				19
Solian	amisulpride	100mg				42
Solian	amisulpride	400mg				60
Soludactone	potassium canrenoate	100mg				3
Soma	carisoprodol	350mg				2
SourceCF Chewables		Chewabl es				3
SourceCF Pediatric Drops		Drops				1
SourceCF Softgels		Softgels				2
Speciality Amino Acid Solution		Solution				5
Stablon	tianeptine sodium	12,5mg				8
Sterile Talc Powder	Talc	5g	USA			44
Steritalc	large size sterile talc powder	4g	USA			6
Sterogyl 15 "H"	ergocalciferol	6000001U/1,5 ml				25

Subutex Sublingual Tablets	buprenorphine hydrochloride	2mg	USA			68
Subutex Sublingual Tablets	buprenorphine hydrochloride	400µg	USA			5
Subutex Sublingual Tablets	buprenorphine hydrochloride	8mg	USA			71
Sucraid	sacrosidase	8500IU/ ml	USA	Europe	ORPHA89109	14
sulfadiazine		500mg	USA			44
sulfamethoxazole and trimethoprim		trimetho prim				3
Sulfamylon	mafenide acetate	50g	USA			23
Sulfamylon Cream	mafenide acetate cream	20Z	USA			21
Sulfamylon Cream	mafenide acetate cream	40Z	USA			2
Sustiva	efavirenz	30mg/ml				3
Synastone	methadone hydrochloride	10mg/ml - 1 ml Ampoule(s)				45
Synastone	methadone hydrochloride	50mg/ml - 1 ml Ampoule(s)				23
Synastone	methadone hydrochloride	10mg/ml - 5ml Ampoule(s)				2
Synercid	quinupristin and dalfopristin					6
Syprine	trientine hydrochloride	250mg	USA	Europe	ORPHA24924	118
Targretin	bexarotene	1% - Eisai Inc.	USA			2
Targretin	bexarotene	75mg - Eisai Inc.	USA			10
Targretin	bexarotene	1% - Valeant				1

Targretin	bexarotene	75mg - Valeant				7
Tasmar	tolcapone	100mg				21
Taurolin	taurolidine	2%				14
Teflaro	ceftaroline fosamil	600mg				8
Tepadina	thiotepa	100mg	USA	Europe	ORPHA86785	67
Tepadina	thiotepa	15mg	USA	Europe	ORPHA86785	30
Testred C Ill	methyltestosterone	10mg				2
Thiola	tiopronin	100mg	USA		ORPHA25073	75
thioridazine hydrochloride		25mg				22
Thyrel	protirelin	0,2mg/ml				23
Tiapride	tiapridal	100mg				1
Tikosyn	dofetilide	125µg				176
Tikosyn	dofetilide	250µg				259
Tikosyn	dofetilide	500µg				221
Tilade CFC-free inhaler	nedocromil sodium					1
Timoptic	timolol maleate	0,005				57
trastuzumab emtansine	T-DM1	160mg				56
Travatan	travoprost ophthalmic solution	0,00004				3
Trecator	ethionamide	250mg				16
Treosulfan	treosulfan	5g	USA	Europe	ORPHA90799	1
triCitrasol	trisodium citrate	46,70%				4
Triostat	liothyronine sodium	10µg/ml	USA			1

Tript-OH	L-5-hydroxytryptophan	100mg				4
Tript-OH	L-5-hydroxytryptophan	50mg				7
Tript-OH	L-5-hydroxytryptophan	25mg				2
Trisenox	arsenic trioxide	1 mg/ml	USA	Europe	ORPHA41289	75
trisodium zinc pentetate	Zn-DTPA	211mg/ml				1
Trobicin	spectinomycin hydrochloride	2g				4
Twin lab Liqui-E (water soluble vitamin E)						21
Ultracain D (epinephrine free)	articaine hydrochloride	40 mg/ml				1
Unasyn		3g				1
uridine triacetate		250g				1
Uvadex	methoxsalen	2µg/ml	USA	Europe	ORPHA81882	76
Valdoxan	agomelatine	25mg				40
Vastarel	trimetazidine	35mg				2
Ventavis	iloprost	10µg/ml			ORPHA34113	3
Vercyte	pipobroman	25mg				11
Videx	didanosine	4g				4
Viibryd	vilazodone	10mg				1
Viramune	nevirapine hemihydrate	10mg/ml				84
Virazole	ribavirin	0,1g/ml			ORPHA90805	18
*VIREAD	tenofovir disoproxil fumarate	250mg	USA			2
Virgan	ganciclovir	0,15%	USA			2
vismodegib		150mg				3

Vistide	cidofovir	75mg/ml				46
Vitamin E	alpha-tocopherol acetate	2 ml				2
Viviant	bazedoxifene	20mg				3
voclosporin		10mg		Europe	ORPHA317318	3
voclosporin		5mg		Europe	ORPHA317318	3
Volumen	barium sulfate	0,10%				1
Voraxaze	glucarpidase	1000U	USA		ORPHA394551	12
Wellbutrin Ir	buproprion	75mg				1
Wycillin	penicillin g procaine suspension	1200000 U				1
Xenbilox	chenodeoxycholic acid	250mg		Europe	ORPHA41421	9
Xifaxan	rifaximin	550mg	USA			770
Yttrium-90 Citrate CIS Bio International						2
Zaltrap	aflibercept	25mg/ml				2
Zanosar	streptozocin	1 g				34
Zemplar	paricalcitol	5µg/ml				3
Zentel	albendazole	200mg	USA		ORPHA24928	1
Zentel	albendazole	400mg	USA		ORPHA24928	212
Zerit	stavudine	200mg				6
Zonegran	zonisamide	100mg				44
Zonegran	zonisamide	50mg				6
Zovirax	acyclovir	3%				159

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